Research Article

A randomised prospective observational study comparing outcomes of labour induction and augmentation between high dose oral misoprostol and intracervical dinoprostone

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Abstract

Introduction: Induction of labour is one of the most commonly practiced interventions in obstetrics all over the world with incidence rates between 10-25% in industrialized countries. Misoprostol, a synthetic prostaglandin analogue, is an effective agent for inducing uterine contractions. We undertook this study to compare the efficacy of high dose (50mcg) oral misoprostol and intracervical dinoprostone gel in induction of labour and compare the safety of the drugs in induction of labour.

Methods: This Prospective Comparative Observational study was carried out at our tertiary care Saifee hospital, Mumbai from March 2015 till May 2016, among 480 women attending antenatal clinics. 240 women received misoprostol 50 mcg orally every 3 hours for a maximum of 6 doses and rest 240 received dinoprostone gel 0.5mg intra-cervically or intra-vaginally every 6 hours for maximum of 3 doses.

Results: The induction to delivery interval was significantly longer in the dinoprostone group (15.13 hours versus 12.69 hours) (p<0.02). 128 (53.3%) of the patients in the dinoprostone group and 86 (35.8%) in the misoprostol group required oxytocin augmentation. There was a significant difference in the proportion of oxytocin requirement between the study groups (p<0.02). No adverse perinatal outcome or perinatal mortality was noted in both the groups.

Conclusion: Oral misoprostol appears to be more effective than dinoprostone gel in the induction of labour with low induction to delivery time and low oxytocin requirement. It can be used in a low resource setting for induction of labour with vigilant monitoring.
Preferred method of induction of labour was Intracervical or vaginal dinoprostone unless there are specific clinical reasons for not using it. On the other hand, dinoprostone has some limitations like cost factor and need for storage facilities at low temperature. This led to the search for an alternative to overcome these limitations. Misoprostol, a synthetic prostaglandin analogue, is an effective agent for inducing uterine contractions that can be used for induction of labour. It can be administered orally, vaginally or sublingually [6]. There is widespread controversy and misunderstanding among clinicians surrounding the safety, efficacy, and preference in the use of misoprostol and dinoprostone for cervical ripening [7-12]. One clinician may swear by a particular method, while a colleague refuses to use it because of its cost, risk/benefit profile, time, or personal experience. Clinical management decisions vary not only from hospital to hospital, but even among providers within the same setting, as indicated in the clinical case here. Management decisions are based on a large number of factors, including institutional protocol, provider preference, patient preference, potential risks and side effects, cost, FDA approval, and medication availability; and not necessarily guided by evidence-based practice. Hence, we undertook this study to compare the efficacy of high dose (50mcg) oral misoprostol and intracervical dinoprostone gel in induction of labour and compare the safety of oral misoprostol and intracervical dinoprostone gel in induction of labour.

Materials and methods

This randomized prospective comparative observational study was carried out at our tertiary care Saifee hospital, Mumbai from March 2015 till May 2016, among women attending antenatal clinic, satisfying the inclusion and the exclusion criteria. Saifee hospital, Mumbai is a tertiary private health centre where around 1500 women are delivered annually. Patients coming for antenatal care and follow up who were judged to benefit from termination than expectant management were recruited in the study. Labour monitoring and delivery was done as per hospital protocol. All the women were explained about the study, intervention and its possible outcome. Women were included in the study after informed consent was taken.

Women with singleton pregnancy with vertex presentation at term or post-term gestation with reactive NST, intact membranes and BISHOP’s score less than 6 were included in the study. Patients with previous uterine surgeries, multiple pregnancies, vaginal bleeding in second half of pregnancy (Placenta previa/abruption placenta), history of asthma, glaucoma, heart disease, conditions which are absolute indication for LSCS e.g. cephalopelvic disproportion, malpresentation, etc. were excluded from the study.

Randomisation was done by sealed envelope system. The clinicians were given treatment allocations within sealed envelopes which were generated randomly. Once a patient has consented to enter the study, the allocated treatment regimen was given as per contained in the sealed envelope.

Sample size calculation

A randomized study demonstrated that 65.7% of patients who were induced with misoprostol (50 µg 6-hourly) has shorter duration of labour, higher rate of vaginal delivery within 24 hours from induction as compared to 54.2 % in patients induced with dinoprostone (1–2 mg 6-hourly) [13]. Taking these values as reference, we determined the sample size required to demonstrate a significant difference in efficacy between the two drugs to be 472 which would be randomized to two groups with equal number of patients. (At 2% level of significance and 90% power of study).

Methods of induction

A total of 513 patients were enrolled in the study. Out of these, 33 patients were excluded from study. 4 patients had previous uterine surgeries, 12 had multiple pregnancies, 6 had history of vaginal bleeding, 2 patients had history of asthma, 2 were known cases of cardiac disease and 7 had cephalopelvic disproportion. Hence a total of 480 patients satisfying the inclusion criteria were induced with misoprostol and dinoprostone as per the method contained in the sealed envelope. According to our Hospital protocol, following regimes were used:

Group I patients: Misoprostol 50 mcg (2 tablets of 25mcg) administered orally every 3 hours for a maximum of 6 doses in 240 patients.

Group II patients: Dinoprostone gel 0.5mg intra-cervically or intra-vaginally every 6 hours for a maximum of 3 doses in 240 patients.

In both groups, continuous fetal heart rate monitoring (CEFM) was done by Philips Avalon FM20 monitor in all cases. The BISHOP score of >8 was considered as successful induction. If spontaneous rupture of membrane has already not occurred, artificial rupture of membranes was being done once cervix was 80% effaced and 3cm dilated. Oxytocin used to be started 2 hours after the last dose of misoprostol or 4 hours after the last dose of dinoprostone gel for augmentation of labour in all patients as per standard protocol at our institution. In patients who had spontaneous rupture of membranes during the process of induction, the next dose of drug in both the groups were delayed for two hours. If there is no spontaneous augmentation of labour during this period, drug for induction is started again until the desired BISHOP’s score is reached in absence of any other complications. Labour was monitored with a partogram.

Outcome variables

Primary outcome measured was time from the application of the first dose to the delivery of the fetus. Secondary outcomes measured were labour and neonatal outcomes. Labour outcomes included maternal age, parity, gestational age, indication of induction, number of doses required, mode of delivery, presence of uterine hyperstimulation with or without abnormalities in the FHR, staining of the amniotic fluid with meconium, requirement for augmentation with oxytocin, neonatal outcomes, APGAR score at 5 minutes after birth,
necessity for admission to the neonatal intensive care unit (NICU), and perinatal mortality rate.

**Statistical analysis**

For the calculation of significance of the primary outcome parameter, independent t-tests for the comparison of two means from independent samples were being used. The value of p <0.02 was considered significant. Results were expressed as number, percentages, range and mean ± SD range. Student’s t-test was used for comparing means of two groups and the Chi-Square test for analysing categorical data. Statistical analysis was done using SPSS software for Windows version 20.0.

**Results**

480 patients requiring induction of labour were studied who satisfied the inclusion criteria out of which 240 patients received intracervical Dinoprostone gel 0.5mg every 6 hours for maximum of 3 doses and other 240 received oral tablet Misoprostol 50 mcg every 3 hours for maximum of 6 doses for labour induction.

Majority of the cases were between 21 to 30 years of age (76.6% in the dinoprostone group vs. 78.3% in the misoprostol group. Minimum age was 18 years and maximum age being 37 years. There was no significant difference between the age of two study groups (p=0.764). No statistically significant difference was seen in the distribution of parity(p=0.195) and gestational age (p=0.064) in the two study groups. There were 65% and 58.3% of nulliparous patients in dinoprostone and misoprostol groups respectively. 66.7% and 55.0% of patients were between 37-40 weeks’ gestation in dinoprostone and misoprostol groups respectively. The most common indication for induction was prolonged pregnancy in both the groups followed by gestational hypertension and IUGR combined; most of the cases were between 21 to 30 years of age (45%) as compared with dinoprostone (33.3%) whereas gestational hypertension and IUGR combined; most of the cases were induced with misoprostol (45.0%) as compared with misoprostol (38.3%) (Table 1).

Majority of the patients in the dinoprostone group i.e. 84 (70%) required 2 doses while in the misoprostol group 50 (41.7%), 32 (26.7%), 20 (16.7%) patients required 3, 2 and 4 doses respectively. The mean dosage required in the dinoprostone group is 1.93 and the misoprostol group is 3.05 (Table 2).

The mean induction to delivery interval was longer with dinoprostone group i.e. 15.13 hours in the dinoprostone group and 12.69 hours in the misoprostol group with significant difference (p value < 0.02) (Table 3).

Vaginal delivery rate was higher in the misoprostol group and caesarean delivery rate was higher in the dinoprostone group however they did not reach statistical significance Caesarean delivery rate was 26.7% and 21.7% in dinoprostone and misoprostol groups respectively (Table 4).

The incidence of uterine hyperstimulation was seen higher in the misoprostol group i.e. 16 (6.7%) as compared to dinoprostone group i.e. 4 (1.7%) with no statistical significance. The incidence of fetal distress evidenced from meconium staining of liquor along with nonreassuring fetal status was higher in misoprostol group i.e. 40 (16.7%) as compared to dinoprostone group i.e. 28 (11.7%) with comparable significance. Requirement of oxytocin augmentation was higher in the dinoprostone group. 128 (53.3%) patients in the dinoprostone group and 86 (35.8%) patients in the misoprostol group required oxytocin augmentation. (Table 5). There was a significant difference in the proportion of oxytocin requirement between the study groups (p value < 0.02).

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**Table 1:** Distribution of Indication of Induction of Labour of Study Subjects by Intervention Method.

| Indication for induction | Study Group | Total |
|--------------------------|-------------|-------|
|                         | Dinoprostone| Misoprostol|  |
| Prevention of *prolonged pregnancy (Induction of labour between 41+0 and 42+0 weeks) [23] | Number | 80 | 108 | 188 |
| % | 33.3% | 45.0% | 39.2% |
| Gestational hypertension* | Number | 56 | 56 | 112 |
| % | 23.3% | 23.3% | 23.3% |
| FGR* | Number | 52 | 36 | 88 |
| % | 21.7% | 15.0% | 18.3% |
| GDM* | Number | 36 | 28 | 64 |
| % | 15.0% | 11.7% | 13.3% |
| BOH | Number | 4 | 8 | 12 |
| % | 1.7% | 3.3% | 2.5% |
| Prolonged latent phase of labour | Number | 12 | 4 | 16 |
| % | 5.0% | 1.7% | 3.3% |
| Total | Number | 240 | 240 | 480 |
| % | 100.0% | 100.0% | 100.0% |

*Definitions: Prolonged pregnancy: A pregnancy continuing beyond 294 days (42 completed weeks) [24]. Gestational hypertension: Gestational hypertension is defined as having a blood pressure greater than 140/90 on two separate occasions at least 6 hours apart [25]. Fetal growth Restriction (FGR): Estimated fetal weight <10th centile for gestational age) [26]. Gestational Diabetes Mellitus (GDM): It is defined as glucose intolerance that was not present or recognized prior to pregnancy [27].

**Table 2:** Number of Doses Required for Induction of Labour by Intervention Method.

| Number of doses | Study Group | Total |
|----------------|-------------|-------|
|               | Dinoprostone| Misoprostol|  |
| 1 | Number | 44 | 12 | 56 |
| % | 18.3% | 5.0% | 11.7% |
| 2 | Number | 168 | 64 | 232 |
| % | 70.0% | 26.7% | 48.3% |
| 3 | Number | 28 | 100 | 128 |
| % | 11.7% | 41.7% | 26.7% |
| 4 | Number | 0 | 40 | 40 |
| % | 0.0% | 16.7% | 8.3% |
| 5 | Number | 0 | 12 | 12 |
| % | 0.0% | 5.0% | 2.5% |
| 6 | Number | 0 | 12 | 12 |
| % | 0.0% | 5.0% | 2.5% |
| Total | Number | 240 | 240 | 480 |
| % | 100.0% | 100.0% | 100.0% |

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Citation: Nath B (2020) A randomised prospective observational study comparing outcomes of labour induction and augmentation between high dose oral misoprostol and intracervical dinoprostone. J Gynecol Res Obstet 6(2): 040-045. DOI: https://dx.doi.org/10.17352/jgro.000084
Mean APGAR score at 5 minutes was almost the same in both the groups i.e. 8.83 and 7.3 in dinoprostone and misoprostol groups respectively. However, 4(1.7%) in each group had APGAR scores of less than 7. 24 (10%) babies in the misoprostol group and 8 (3.3%) in the dinoprostone group had a score of 7 (Graph I). However, there was no adverse perinatal outcome.

NICU admission rate was 10% in the misoprostol group as compared to 6.7% in the dinoprostone group. This higher rate of NICU admission in the misoprostol group did not reach statistical significance (p >0.02). No perinatal mortality was present in both the groups.

### Table 3: Induction to delivery interval.

| Study Parameter | Misoprostol Group | Dinoprostone Group |
|-----------------|-------------------|--------------------|
|                 | Mean              | Std. Deviation     | Median             | IQR   |
| I-D interval (mins) | 761.12            | 285.09             | 722.50             | 335.00 |
| I-D interval (Hrs)  | 12.69             | 4.75               | 12.04              | 5.58   |
| Birth wt (Kg)      | 2.81              | 0.48               | 2.79               | 0.68   |
| APGAR (5 mins)     | 8.73              | 0.71               | 9.00               | 0.00   |

### Table 4: Mode of delivery by intervention method.

| Mode of delivery | Study Group | Total |
|------------------|-------------|-------|
|                  | Dinoprostone | Misoprostol | |
| Vaginal          | Number      | 176    | 183    | 364    |
|                  | %           | 73.3%  | 78.3%  | 75.8%  |
| LSCS             | Number      | 64     | 52     | 116    |
|                  | %           | 26.7%  | 21.7%  | 24.2%  |
| Total            | Number      | 240    | 240    | 480    |
|                  | %           | 100.0% | 100.0% | 100.0% |
| Chi-Square test  | Value       | DF     | P Value| Association is |
| Pearson Chi-Square| 0.818        | 1      | 0.366  | Not Significant |
| Fisher’s Exact Test| 0.451        |        |        | Not Significant |

### Table 5: Oxytocin Requirement by Intervention Method.

| Oxytocin Requirement | Study Group | Total |
|----------------------|-------------|-------|
|                      | Dinoprostone | Misoprostol | |
| Yes                  | Number      | 128    | 86     | 214    |
|                      | %           | 53.3%  | 35.8%  | 44.6%  |
| No                   | Number      | 112    | 154    | 266    |
|                      | %           | 46.7%  | 64.2%  | 55.4%  |
| Total                | Number      | 240    | 240    | 480    |
|                      | %           | 100.0% | 100.0% | 100.0% |
| Chi-Square test      | Value       | df     | P Value| Association is |
| Pearson Chi-Square   | 7.437       | 1      | <0.02  | Sig     |
| Fisher’s Exact Test  |             |        |        | <0.02   | Sig     |

**Discussion**

Although Dinoprostone gel is the preferred pharmacologic method of induction of labour [1], because of its cost and storage requirement the search for an effective, easily stored, affordable labour inducing agent has led to the use of misoprostol. The efficacy of vaginal misoprostol for induction of labour was confirmed by many investigators since the 1990s. The general concern in the use of intravaginal misoprostol for induction of labour was significant incidence of uterine tachysystole and hyperstimulation and potential of fetal jeopardy. The dose was titrated and lower doses of 25 μg were found to be effective while the hyperstimulation and meconium passage were found less frequently [14].

In our present study the mean induction to delivery interval (primary outcome of this study) was significantly less in the misoprostol group. Similar to our study, Nanda S, et al. in 2007 demonstrated that the mean induction to delivery interval was five hours shorter in the misoprostol group (13.30 vs. 18.53 hrs. p<0.05) [15]. Some other studies have demonstrated contradictory results. Prager M, et al. [16] 2008 (16.5 vs.16.16hrs), Gregson S, et al. 2005 (15 hrs in both groups) found that both misoprostol and dinoprostone has equal induction to delivery time [16]. Some studies have shown the misoprostol to have even more induction to delivery time than dinoprostone. Gemund N, et al. (2004), in their study concluded that the median induction-to-vaginal delivery interval was approximately 6 hours longer in the misoprostol group (25 versus 19 hours, p < 0.05) [17]. However, they used pulverized Misoprostol with cellulose in a capsule which could have reduced the efficacy. Various studies have shown different results regarding induction to delivery time. This variation can be explained to a little extent by individual variation and technique of application of putting Dinoprostone intracervical or misoprostol intravaginally in the posterior fornix. More standardized study is required in this regard.

Oxytocin requirement in our present study was significantly lower in the misoprostol group. Blanchette HA, et al. Demonstrated oxytocin requirement was more in Dinoprostone group (81.5% vs. 63.5% p value 0.24), which is consistent with our study [18]. In contradiction to this, some studies have shown a similar rate of Oxytocin requirement. In the study by Gregson S, et al. 2005, the requirement of oxytocin augmentation
was similar in both groups however fewer (36%) required augmentation [16]. Girija S, et al. 2011 also demonstrated a similar requirement (35.4% vs. 34%) of oxytocin [19]. Gemund N, et al. 2004, demonstrated oxytocin requirement (45% vs. 58% p value 0.13) more in the misoprostol group but was not significant [17].

Vaginal delivery rate in our study was a little higher in the misoprostol group compared to the dinoprostone group with no statistical significance. Blanchette HA, et al. [18] 1999 (74.4 vs 77.8%), Gregson S, et al. [16], 2005 (74 vs 76%) in their studies showed more vaginal delivery rate in the dinoprostone group but was not significant. But some studies like Gupta N, et al. 2006 demonstrated higher total vaginal delivery rate (74% vs.88%) and spontaneous vaginal delivery rate (68% vs. 86% p value <0.05 statistically significant) with misoprostol which was statistically significant [20]. Similar higher vaginal delivery rate with misoprostol was found in the study of Murthy BK, et al. 2006 (62.85% vs. 78.37 %) [21]. Overall if we see, most of the studies showed that vaginal delivery rate is more with misoprostol as compared to dinoprostone.

Uterine hyperstimulation in our study was 1.7% and 6.7% in Dinoprostone and Misoprostol groups respectively. Study conducted by Gemund N, et al. 2004, demonstrated an incidence of 8% in both groups [17]. Results of our study were consistent with other studies by Gupta N, et al. [20] 2006 (2% vs. 4%), Murthy BK, et al. [21] 2006 (2.85% vs.5.4%) and Tan TC, et al. [22] 2010 (3.5 %) in both groups.

Meconium staining of liquor in the present study was 11.7% and 20% in the dinoprostone and misoprostol groups respectively. The rate was higher in the Misoprostol group but statistically not significant. Contrary to our study Gemund N, et al [17] 2004, reported a very high incidence of meconium staining of liquor in both the groups (42% vs. 46%). Other studies Gupta N, et al. [20] 2006 (12% vs. 8%) and Tan TC, et al. [22,23] 2010 (0% vs. 3.5%) reported lower incidence in the misoprostol group.

Mean APGAR score was similar in both the groups and the incidence of APGAR score less than 7 was 1.7% in both the groups. Similar results have been reported in the studies by Blanchette HA, et al. [18] 1999 (1.2% vs. 1.4%), Gemund N, et al. [17], 2004 (2% in each group), Gregson S, et al. 2005 [16] (1% in each group).

The NICU admission rate in the present study was higher in the misoprostol group with no statistical significance. Wing DA, et al. [12] 1995 (8% vs. 9.6%) reported similar results. Other studies Blanchette HA, et al. [18] 1999 (6.2% vs. 4.8%), Gregson S, et al. [16] 2005 (2% vs. 1%), Girija S, et al. [19] 2011 (0.6% vs 0%) have reported very low rates of NICU admission. Most studies have reported higher admission rates with dinoprostone compared to misoprostol contrary to the findings of our study. No perinatal mortality was associated with our study.

Limitation

The study was undertaken in a private setup institution which has low caseload referrals with doctor patient ratio being 1: 2. Patients were monitored with continuous CTG with excellent nursing care. The accessory components of consideration associated with the birthing process viz fear, stress, anxiety and dissatisfaction were eased off with sympathetic counselling and compassionate approach. This could probably exert considerable impact on the attitude and behaviourism of the labouring mother. Caution should be taken while adopting this high dose regimen in public sector institutions and places where load of cases is high and strict monitoring may not be possible.

Conclusion

Oral Misoprostol appears to be more effective than dinoprostone gel in the induction of labour with low induction to delivery time and low oxytocin requirement. Misoprostol is a cheap alternative to dinoprostone gel in the induction of labour and can be used in a low resource setting for induction of labour. Extreme caution should be taken while using this high dose induction regimen of misoprostol in institutions with a low doctor patient ratio.

Contributorship statement

1. Siddhi Tatwadiya: Planning, Conduct, Acquisition, Interpretation and Analysis of data.
2. Banashree Nath: Planning, Data analysis, Interpretation of data, Manuscript drafting.
3. Harsha S. Gaikwad: Planning, Input and revision of manuscript.
4. Kashika Nagpal: Interpretation of data, Input and revision of manuscript.

Ethical clearance

Ethics Committee Approval Was Secured For The Study From Institutional Review Board (Irb), Mumbai

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