A Prospective Comparative Study of Mifepristone and Misoprostol vs Misoprostol Alone for Induction of Labor in Intrauterine Fetal Death

Aarzoo Hoda1, Nasreen Noor2, Shazia Parveen3, Manazir Ali4, Ummay K Kulsoom5

ABSTRACT

Introduction: Intrauterine fetal death (IUFD) is an important indicator of maternal and perinatal health of a given population.

Aim and objective: The objective of the study was to assess the efficacy of mifepristone and misoprostol vs misoprostol alone for induction of labor in IUFD and to determine risk-benefit ratio.

Materials and methods: The present study was a prospective observational analytical study which was conducted in the Department of Obstetrics and Gynecology, JNMCH, Aligarh, from January 2018 to January 2021 and includes 110 pregnant women with confirmed IUFD on USG. After taking informed consent, a predesigned pro forma was used to collect relevant sociodemographic profile, detailed logical history, and examination from all those participating in the study.

Results: Age (mean ± SD) was 25.98 ± 4.49 vs 25.69 ± 4.78 years, parity was 2.31 ± 1.3 vs 2.44 ± 1.61, and gestational age was 31.04 ± 6.89 vs 32.71 ± 5.17 weeks in group I and group II, respectively. Modified Bishops score was >6 in 35 (63.64%) vs 32 (14.55%) women, mean dose of misoprostol required was 0.95 ± 1.5 vs 2.64 ± 1.89, mean induction labor interval was 2.42 ± 7.53 hours, and mean induction to delivery interval was 6.68 ± 16.61 hours in group I and group II, respectively, and the difference was found to be statistically significant. Mean birth weight was 1431.35 vs 1758.60 g, respectively, in the two groups. Four women (7.27%) in group I and 17 women (30.9%) in group II required augmentation with oxytocin which is statistically significant. Nausea, vomiting, loose stools, and hyperthermia were recorded as adverse effects. Among the identifiable causes, abruption was the most common cause in group II, whereas anemia and preeclampsia in group I.

Conclusion: The combination of mifepristone with misoprostol was more effective for the induction of labor in IUFD, in terms of lesser amount of misoprostol dosage, oxytocin augmentation, improvement in modified Bishops score, and shorter induction labor and delivery interval when compared to misoprostol alone. Both the regimens were equally safe and easy to administer.

Keywords: Intrauterine fetal death, Labor induction, Mifepristone, Misoprostol.

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INTRODUCTION

When an intrauterine fetal death (IUFD) is discovered, the physician has no choice but to terminate the pregnancy. For both the parents and the managing physician, delivering an IUFD is a pitiful and stressful experience. The uterus is usually not particularly susceptible to the usual induction procedures before term; therefore, it can be a frustrating task for a physician.

There were 2.65 million IUFD worldwide in 2015, with 98% coming from underdeveloped nations.1

The National Center for Health Statistics defines fetal death as “death before the complete expulsion or extraction from its mother of a product of human conception, irrespective of the duration of pregnancy and which is not an induced termination of pregnancy,” according to the 2003 revision of the procedures for coding cause of fetal death under ICD-10.

The fetus does not breathe or show any other signs of life following such expulsion or extraction, such as heartbeat, umbilical cord pulsation, or voluntary muscle activity, which are all indicators of IUFD. The fetal heartbeat should be identified from transient cardiac contractions, and breathing should be distinguished from passing gasps.2 3

In the case of intrauterine fetal mortality, a variety of methods of induction of labor have been tried. Because of its low cost; room temperature stability; and convenience of administration, misoprostol, a prostaglandin E1 analog, is favored. Mifepristone is a steroid that inhibits progesterone function at the receptor level and is commonly used to end pregnancies in the first and second trimesters.4–6

Mifepristone sensitizes the uterus to prostaglandin action and ripens the cervix when given before. Because of mifepristone’s method of action on the cervix, lesser doses of misoprostol are necessary to induce labor.

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Fever, nausea, vomiting, dizziness, diarrhea, and headache are all frequent side effects of misoprostol. The most dangerous side effect of misoprostol is aberrant uterine action, such as uterine hyperstimulation, which can result in uterine tachysystole and rupture. 

Various therapy options for terminating a pregnancy due to intrauterine death have been proposed, but an appropriate strategy for inducing labor has yet to be determined. As a result, the current study compares the efficacy of mifepristone and misoprostol vs misoprostol alone for induction of labor in IUFD.

Materials and Methods
The present study was a prospective observational clinical study and was conducted in the Department of Obstetrics and Gynecology, JNMCH, AMU, Aligarh, during 2018–2020 after ethical clearance. All recruited women were counseled and enrolled after informed consent. A total of 110 pregnant women (primigravida and multigravida) attending an antenatal clinic, outpatient department, or those admitted in the labor wards, with IUFD (confirmed by an ultrasonographic evaluation) with a gestational age more than 20 weeks, were enrolled in this study from 2018 to 2020 and they belong to these two groups:

- Group I (combination regimen)—women received 200 mg mifepristone orally and misoprostol after 24 hrs. Women with a gestational age of 20–26 weeks induction with 100 µg of oral misoprostol every 6 hours for a maximum of four doses. If the first dose did not lead to effective contractions, the subsequent dose was repeated. Beyond 26 weeks, 50 µg was given every 4 hours up to six doses.
- Group II (misoprostol group)—women with a gestational age of 20–26 weeks received 100 µg of oral misoprostol every 6 hours for a maximum of four doses. Beyond 26 weeks, 50 µg was given every 4 hours up to six doses. If the first dose did not lead to effective contractions, the subsequent dose was repeated.

Successful treatment was defined as delivery within 72 hours of the first misoprostol dose. Descriptive data analysis was done by percentages and mean ± SD (standard deviation).

Inferential statistics were applied using Chi-square test and Fischer’s test for qualitative variables and Pearson’s correlation and t-test for quantitative variables using SPSS.

Results
The prospective study was conducted in the Department of Obstetrics and Gynecology, JNMCH, AMU, Aligarh, during 2018–2021 after ethical clearance. A total of 114 pregnant women were participated in the study after fulfilling the inclusion and exclusion criteria.

Table 1 shows that the age (mean ± SD) of women included in group I and group II was 25.98 ± 4.49 and 25.69 ± 4.78 years, respectively. Mean ± SD of parity and gestational age was 2.31 ± 1.3, 2.44 ± 1.61, 31.04 ± 6.89, and 32.71 ± 5.17 weeks in group I and group II, respectively. However, the difference of demographic and obstetrics parameters in both groups was found to be statistically nonsignificant (p > 0.05).

A maximum number of women in both the groups had Bishops score in the range of 0–3 at the time of admission and the difference was found to be statistically nonsignificant. Preinduction Bishops score (after mifepristone administration) in 36 (65.45%) women in group I was in the range of 4–6 as compared to 38 (69.1%) women in group II who had preinduction Bishops score in the range of 0–3. The difference was found to be statistically significant (p < 0.05). At 12 hours, Modified Bishops score was >6 in 35 (63.64%) women as compared to 32 (14.55%) women in group I and group II, respectively, and the difference was found to be statistically significant. Table 2 depicts the above comparison.

The mean ± SD dose of misoprostol required in group I was 0.95 ± 1.5 and in group II was 2.64 ± 1.89; mean induction labor interval was 2.42 hours in group I as compared to 7.53 hours in group II; and mean induction to the delivery interval was 6.68 vs 16.61 hours in group I and group II, respectively, and the difference was found to be statistically significant. Mean birth weight in group I was 1431.35 ± 843.86 g and in group II was 1758.60 ± 890.29 g, and the difference was found to be statistically nonsignificant (p > 0.05) as shown in Table 3.

Nausea, vomiting, loose stools, and hyperthermia were recorded as adverse effects. No cases of postpartum hemorrhage, uterine tachysystole, ruptured uterus, or any coagulopathy had been noted in both groups. The difference in the side effects of both the groups was found to be statistically nonsignificant (p > 0.05) as depicted in Figure 1.

The majority of women 33 (60%) in group II had maternal causes as compared to 29 (52.7%) in group I, and the difference was statistically significant (p < 0.05). Abruption (22.5%) was the

Table 1: Sociodemographic and obstetric parameters (mean ± SD)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group I</th>
<th>Group II</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>25.98 ± 4.49</td>
<td>25.98 ± 4.49</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Parity</td>
<td>2.31 ± 1.36</td>
<td>2.44 ± 1.61</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>31.04 ± 6.89</td>
<td>32.71 ± 5.17</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Preinduction Bishop score</td>
<td>2.62 ± 1.28</td>
<td>2.69 ± 1.32</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

Table 2: Modified Bishops score of women with time intervals

<table>
<thead>
<tr>
<th>Groups</th>
<th>Modified Bishops score</th>
<th>Preinduction (at admission)</th>
<th>Preinduction (after mifepristone in group I)</th>
<th>After 12 hours of induction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group I</td>
<td>0–3</td>
<td>40</td>
<td>19</td>
<td>04</td>
</tr>
<tr>
<td>(n = 55)</td>
<td>4–6</td>
<td>15</td>
<td>36</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>&gt;6</td>
<td>00</td>
<td>00</td>
<td>35</td>
</tr>
<tr>
<td>Group II</td>
<td>0–3</td>
<td>38</td>
<td>38</td>
<td>15</td>
</tr>
<tr>
<td>(n = 55)</td>
<td>4–6</td>
<td>17</td>
<td>17</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>&gt;6</td>
<td>00</td>
<td>00</td>
<td>08</td>
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</tbody>
</table>

Table 3: Outcome measurement (mean ± SD)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group I</th>
<th>Group II</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean dose of misoprostol</td>
<td>0.95 ± 1.50</td>
<td>2.64 ± 1.89</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Oxytocin augmentation needed</td>
<td>04 (7.27%)</td>
<td>17 (30.9%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Induction labor interval (hours)</td>
<td>2.42 ± 3.49</td>
<td>7.53 ± 7.45</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Induction delivery interval (hours)</td>
<td>6.68 ± 11.50</td>
<td>16.61 ± 12.38</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Birth weight (mean ± SD)</td>
<td>1431.35 ± 843.8</td>
<td>1758.60 ± 890.29</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>
most common cause in group II, whereas anemia (16.4%) and preeclampsia (16.4%) in group I as shown in Figure 2.

**Discussion**

Both groups were comparable in age in our study, and our results were similar in terms of mean age, with no statistically significant difference between them. Both groups had a higher mean gestational age than the current study, although the difference was statistically insignificant. The mean number of doses of misoprostol administered to women in the present study was less in the combination group in comparison with the misoprostol group and this finding is in harmony with the studies. They concluded that pretreatment with mifepristone decreased the number of doses of misoprostol required for women to go into labor. We found a significant decrease in the requirement of misoprostol with prior use of mifepristone that is consistent with the literature that shows decreased prostaglandin requirement in cases where mifepristone was given and also owing to the effective cervical ripening by prior administration of mifepristone.

The mean induction labor interval was more in group II as compared to group I. The difference was found to be statistically highly significant. Comparable results were reported by various studies. But mean induction to delivery interval varies in all the studies. The probable reason is a difference in the dosage and schedule of misoprostol used according to various study guidelines. A significantly shorter induction-delivery interval (IDI) in women who were primed with mifepristone before misoprostol compared with those who were given misoprostol only.

The induction to delivery interval reflects the time interval between the first dose of misoprostol to the expulsion of the fetus. In the present study, mean induction to the delivery interval was less in group I compared to group II and the difference was found to be statistically significant. Mifepristone is an antiprogesterone steroid, which induces cervical ripening and increases uterine activity, thus leading to the expulsion of the fetus. Similar results were also shown by other authors. Most current guidelines recommend a time interval of 36–48 hours of administration between mifepristone and misoprostol. The mechanism for this basis is due to uterine muscle having maximum sensitivity to prostaglandins and its analogs following such an interval. Sindhuri et al., Hemalatha et al., and Trivedi et al. found that combination had shorter induction delivery intervals as compared to misoprostol only regimen, and the difference was found to be statistically significant.

In the present study, a lesser number of women within group I (7.27%) required augmentation with oxytocin as compared to group II (30.9%). The difference within the augmentation with oxytocin required was found to be statistically significant. Gupta et al. and Trivedi et al. found similar results that a lesser number of women required augmentation with oxytocin in group I women as compared to the women in group II. Augmentation with oxytocin was required in 11.5% of women in group II, but no oxytocin was required within the combination group which was against our results. Our results were not consonant with Maheshwari et al. who found that more cases required augmentation with oxytocin in group II than group I; however, the difference decided to be nonsignificant statistically.

Although group II had a slightly greater mean birth weight, the difference was found to be statistically insignificant. Modak et al. reported comparable results, but Arjunan et al. identified a slightly higher mean birth weight in the combination group, which was counter to our findings but not statistically significant.

In the misoprostol group, side symptoms like fever and shivering were more common than in the combined therapy group. According to Panda et al., the two groups did not differ significantly in terms of complications suffered during labor and delivery.

The majority of women in group II have maternal factors of IUFD as compared to group I, and the difference was statistically significant. Abruptio (22.5%) was the most common cause in group II, whereas anemia (16.4%) and preeclampsia (16.4%) in group I.

**Conclusion**

When compared to misoprostol alone, the combination of mifepristone and misoprostol was more effective for the induction of labor in IUFD in terms of less misoprostol dosage, oxytocin augmentation, improvement in Modified Bishops score, and shorter induction labor and the delivery interval. Both regimens were similarly safe, simple to use, and cost-effective.

More study with bigger sample size is needed before standard treatment options for patients with IUFD can be recommended.

**Acknowledgments**

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**Ethical approval:** The study was approved by the institutional ethics committee.
REFERENCES