A COMPARATIVE STUDY OF MIFEPRISTONE AND MISOPROSTOL VERSUS MISOPROSTOL ALONE IN INDUCTION OF LABOUR IN LATE INTRAUTERINE FETAL DEATH

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Article Info: Received 08 January 2021; Accepted 16 February 2021
DOI: https://doi.org/10.32553/ijmbs.v5i2.1756
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Conflict of interest: No conflict of interest.

Abstract

Objective: To compare efficacy, safety and tolerance of combination of Mifepristone and Misoprostol versus Misoprostol alone in induction of labour in late intrauterine fetal death (>24 weeks).

Methods: This prospectively studied included 160 women with late intrauterine fetal death (IUFD) after 24 weeks of gestation and divided the women randomly into two groups each containing 80 women. In Group-A: Mifepristone 200 mg single dose was given and after 24 hrs Tab Misoprostol (intravaginally) administered and repeated 4 hourly upto a maximum of 5 doses, while in Group-B: Only Tab Misoprostol administered intravaginally 4 hourly upto maximum 5 doses. Induction-delivery interval and number of doses of Misoprostol was calculated.

Results: The mean induction-delivery interval in Group-A was 13.02 ± 3.74 hours and in Group-B was 16.09 ± 2.99 hours (p-value <0.0001). Mean doses of Misoprostol required in Group-A was 3.36 ± 1.08 hours and in Group-B was 4.32 ± 0.65 hours (p-value <0.0001).

Conclusion: Combination of Mifepristone and Misoprostol is more effective as comparison to Misoprostol in terms of induction-delivery interval and number of doses of misoprostol required.

Keywords: IUFD, mifepristone, misoprostol, induction of labour, induction-delivery interval.

Introduction

The frequency of intrauterine fetal death with a retained fetus varies, but is estimated to occur in 1% of all pregnancies. The vast majority (over 90%) of women will go into spontaneous labor and deliver within three weeks of the intrauterine death. Expectant management therefore remains an acceptable option in some settings.1

As in IUFD journey of labor pain will be fruitless. So, it is of utmost important to search for the method which can reduce hour of pain in labor of IUFD cases. 2 However, moderate to severe maternal anxiety had been found to occur if labor has failed to start 24 h after diagnosis. Thus, social and maternal desires and moderate risk of maternal complications compel the caregiver to induce labor soon after diagnosis, aiming for a safe and speedy delivery.3

Many methods of induction of labour in intrauterine fetal death have been used. Prostaglandins have changed the scenario in modern obstetrics. Mifepristone if administered before Misoprostol sensitizes the uterus to the action of prostaglandins and ripens the cervix. Due to this effect of Mifepristone on the cervix, lower doses of Misoprostol are required to induce expulsion of fetus. This present study was undertaken to compare the effectiveness and safety of combination regime of mifeprorstone and misoprostol with misoprostol alone.

The antepartum death occurring beyond 28 weeks is termed as intrauterine death. Cause for IUD is not known in 25-35% of cases. Maternal, paternal and fetal conditions are known to result in fetal demise.4 Common causes of IUFD include maternal systemic illness such as diabetes mellitus and hypertension and fetal causes such as infection, immune haemolytic disease, cord accidents, metabolic disorders, malformation and placental dysfunction.5

The aim of present study is to compare the efficacy and safety of combination of Mifepristone and Misoprostol versus misoprostol alone.

Material and Methods

This prospective study includes total 160 women with IUFD after 24 weeks of gestational age. The study was carried out in the Department of Obstetrics & Gynaecology, SMS Medical College, Jaipur in the time period of May 2019 to Nov 2020. All the women were counselled regarding induction and option available for induction. All the cases were subjected to detailed history taking and clinical examination. IUFD was confirmed by USG. Written informed consent was taken. Women with intrauterine fetal death between 24-40 wks of the gestational age were included in the study. The women with Haemoglobin < 8 gm, coagulopathy or anticoagulent therapy, Inherited Porphyria, Glaucoma, Previous caesarean, Multiple pregnancy and in labour were excluded in the study. Women were categorized into two groups randomly. In Group-A : Women received Tabl Mifepristone 200 mg orally followed by the Tab Misoprostol 24 hours
labour per vaginum, dose of which calculated according to gestational age. Gestational age between 24-26 weeks Tabl Misoprostol given 200 µg per vaginum, gestational age between 27-28 weeks misoprostol 100 µg given per vaginum and after 28 weeks 25 µg of misoprostol given, which is repeated every 4 hours till maximum 5 doses, while in Group-B only Misoprostol given dose of which given according to gestational age and maximum 5 doses are given. All doses given pervaginally.

- The blood pressure, pulse rate and temperature were monitored every 4 hourly.
- The cases were closely monitored for the onset of contraction, bleeding, cervical dilatation, side effects each time before insertion of Misoprostol.
- After expulsion, the product of conception was examined and, if incomplete evacuation of the uterus was performed. The decision for evacuation of the uterus was based on the clinical findings.
- The induction-delivery interval was defined as the interval between the time of administration of the first dose of Misoprostol to the time when the fetus aborted.
- Completion was defined as the expulsion of both fetus and placenta in complete if part or whole of the placenta was retained.
- All women were followed for 2 weeks.
- If women fail to deliver within 24 hours after the 1st dose of Misoprostol, 2nd course of Misoprostol was repeated 12 hours after the last dose.
- In case of failure another method was used.
- Both the groups were compared regarding following outcomes: -
  * Acceptability
  * Induction-delivery interval
  * Successful delivery
  * Side effects and complications
  * Total amount of drug required (Tab Misoprostol)
  * Need for evacuation / Manual removal of placenta
  * Inj. Anti-D was given to all Rh-negative pregnancies.
  * Data was analysed.

**Results**
As regard to obstetrics parameter of gestational age in weeks, maternal age, gravida, parity and preinduction Bishop score in both groups were comparable.

**Table 1: Demographic Profile and Obstetric Parameter**

<table>
<thead>
<tr>
<th></th>
<th>Group-A</th>
<th>Group-B</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (in years)</td>
<td>25.74 ± 4.61</td>
<td>25.59 ± 4.7</td>
<td>0.8388</td>
</tr>
<tr>
<td>Gestation Age (in weeks)</td>
<td>33.05 ± 3.37</td>
<td>33.45 ± 3.77</td>
<td>0.4800</td>
</tr>
<tr>
<td>Gravida</td>
<td>1.96</td>
<td>1.98</td>
<td>≥0.05</td>
</tr>
<tr>
<td>Bishop Score</td>
<td>2.91 ± 1.18</td>
<td>3.10 ± 1.13</td>
<td>0.3071</td>
</tr>
</tbody>
</table>

The mean age of women in Group-A was 25.74 ± 4.61 years and in Group-B was 25.59 ± 4.7 years and p-value >0.05 which was not statistically significant. The gestational age in Group-A was 33.05 ± 3.37 weeks and in Group-B was 33.45 ± 3.77 weeks which was also statistically not significant (p-value >0.05). The pre-induction Bishop score in Group-A was 2.91 ± 1.18 and in Group-B was 3.10 ± 1.13, with p-value >0.05 which was also statistically not significant. The mean gravidy in Group-A was 1.96 and in Group-B was 1.98 with p-value >0.05.

**Table 2: The Efficacy of Both Regimen Was Compared by Following Parameters**

<table>
<thead>
<tr>
<th>No. of Doses of Misoprostol Required</th>
<th>Group-A</th>
<th>Group-B</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction-Delivery Interval (in hours)</td>
<td>13.02 ± 3.74</td>
<td>16.09 ± 2.99</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

The mean number of doses of Misoprostol required in Group-A was 3.36 ± 1.08 and in Group-B was 4.32 ± 0.65, with p-value <0.001, which indicates that less number of doses was required in Mifepristone pretreated women. The induction-delivery interval in Group-A was 13.02 ± 3.74 hours and in Group-B was 16.09 ± 2.99 hours which indicates that the induction-delivery interval in Mifepristone pretreated women was less as compared to Misoprostol alone, p-value was highly significant (<0.001).

**Table 3: Distribution of Cases According to Side Effects**

<table>
<thead>
<tr>
<th>Side-effects</th>
<th>Group-A</th>
<th>Group-B</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>45</td>
<td>37</td>
<td>0.2058</td>
</tr>
<tr>
<td>Nausea / Vomiting</td>
<td>28</td>
<td>35.00</td>
<td>0.0170</td>
</tr>
<tr>
<td>Headache</td>
<td>13</td>
<td>16.25</td>
<td>0.1714</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>9</td>
<td>11.25</td>
<td>0.0575</td>
</tr>
<tr>
<td>Fever</td>
<td>10</td>
<td>12.50</td>
<td>0.4990</td>
</tr>
</tbody>
</table>

Common side effect in Group-A and B was pain (56.25% & 46.25% respectively), nausea and vomiting (35.00% & 53.75% respectively), less common side-effect was headache (16.25% & 25.00% respectively), diarrhoea (11.25% & 22.50% respectively) and fever (12.50% & 16.25% respectively). In above mentioned variable p-value was statistically not significant except in nausea and vomiting where the p-value was 0.0170, which was statistically significant.

**Discussion**

The mean number of doses of misoprostol required in Group-A and B were 3.36 ± 1.08 and 4.32 ± 0.65 respectively. The less doses were required in Group-A as compared to Group-B. p-value was <0.0001, which was statistically significant. A study conducted by Modak R et al (2018)³ in which mean doses of misoprostol required in Group-I (Mifepristone and Misoprostol) was 2.41 ± 1.19 and in Group-II (Misoprostol only) was 3.74 ± 0.74. A study done by Hemplatha KR et al (2018)⁴ the number of doses in Group-I (Mifepristone and Misoprostol) required was 1.52 ± 1.14 and in Group-II (Misoprostol only) was 2.76 ± 1.05. However the study done by Abbasi S et al (2017)⁵ the mean number of doses of misoprostol required
in combined group was 1.89 ± 0.96 and in misoprostol only group was 3.41 ± 1.2.

The mean induction-delivery interval in Group-A was 13.02 ± 3.74 hrs and in Group-B was 16.09 ± 2.99 hrs. The mean induction-delivery interval in Group-A was significantly shorter as compared to Group-B (p-value <0.0001). A study was conducted by Lalrinfela et al (2018) in which mean induction-delivery interval in Group-I (Mifepristone and Misoprostol) was 9.6 ± 2.4 hrs and in Group-II (Misoprostol only) was 17.1 ± 3.7 hrs. A study conducted by Modak R et al (2018) in which mean induction-delivery interval in Group-I (Mifepristone and Misoprostol) was 12.45 ± 6.25 hrs and in Group-II (Misoprostol only) was 20.25 ± 7.28 hrs. In a study done by Gupta S et al (2016) where the mean induction-delivery interval in Group-A (Mifepristone and Misoprostol) was 9.6 ± 3.03 hrs and in Group-B (Misoprostol only) was 16.2 ± 6.2 hrs, which was similar to my study.

The most common side-effect in Group-A was pain (56.25%) and in Group-B was nausea and vomiting (53.75%). Other side effect in Group-A was nausea and vomiting (3.50%), followed by headache (16.25%), followed by fever (12.50%) and diarrhoea (11.25%). In Group-B other side effects were pain (46.25%), followed by headache (25.00%), followed by diarrhoea (22.50%) and fever (16.25%). In above mentioned side-effects p-value was not statistically significant except in nausea and vomiting, which were more common in Group-B as compared to Group-A (p-value < 0.05), which was due to less doses required in Group-A as compared to Group-B. A study conducted by Modak R et al (2018) in which side-effects in Group-I (Mifepristone and Misoprostol) and Group-II (Misoprostol only) were nausea (3.17% and 1.59% respectively), pyrexia (1.59% and 3.17% respectively), shivering (3.17% and 8.77% respectively), nil (92.07% and 84.21% respectively). A study was conducted by Hemalatha KR et al (2018) in which the side effects in Group-I (Mifepristone and Misoprostol) and Group-II (Misoprostol only) was nausea (24.1% and 10% respectively), diarrhoea (6% and 4% respectively), fever (22% and 32% respectively) and headache (8% and 6% respectively). In a study conducted by Gupta S et al (2016) in which adverse effect in Group-A (Mifepristone and Misoprostol) was 10% as compared to Group-B (Misoprostol only) (16.7%). Shah PM et al (2015) conducted a study in which the side-effects in Group-I (Mifepristone and Misoprostol) and II were nausea (35.4% and 50% respectively), vomiting (22.5% and 21.4% respectively), fever (0% and 4.7% respectively), headache (3.2% and 4.7% respectively).

**Conclusion**

From our study, we conclude that the combination of mifepristone with misoprostol significantly reduces the induction-delivery interval and also have fewer side-effects as less number of doses of misoprostol are required. Where the mifepristone is not available or affordable, misoprostol alone has also been shown to be effective, although a higher total number of doses are required and acceptability is lower than the combined regime. Therefore whenever possible, the combined regimen should be used.

**References**