Abstract

Context: Intrauterine fetal death (IUFD) causes emotional distress and could result in intrauterine infection. In view of these complications, medical induction is recommended, if it is safe. Aim: The aim of this study was to compare the efficacy and safety of a combination of mifepristone and misoprostol with oral misoprostol alone for induction of labor in IUFD. Settings and Design: This is a randomized placebo-controlled trial conducted at a tertiary care teaching hospital in southern India. Patients and Methods: We recruited 72 women with IUFD in a singleton pregnancy after 28 weeks with intact membranes. Thirty-six women received oral placebo followed by misoprostol. In other group, 36 women received 200 mg oral mifepristone followed by misoprostol (both groups received 50 μg orally 4th hourly up to 5 doses). The interval between mifepristone/placebo and the first dose of misoprostol was 24 h. Results: Successful delivery occurred within 72 h in 31 of 36 (86%) women who received mifepristone before misoprostol and in 28 of 36 (78%) women who received only misoprostol (P = 0.541). Median (interquartile range) induction to delivery interval was 3.5 (2–5) and 4 (3–5) h in the combination group and misoprostol group, respectively (P = 0.465). Conclusions: Addition of mifepristone to misoprostol appears to be marginally more effective than misoprostol alone for induction of labor in intermediate and late IUFD, although the differences were not statistically significant.

Keywords: Intrauterine fetal death, mifepristone, misoprostol, randomized controlled trial

INTRODUCTION

Intrauterine fetal death (IUFD) is diagnosed when the fetus dies in the uterus after 28 weeks of gestation. It is a relatively common occurrence. Common causes of IUFD include maternal systemic illnesses such as diabetes mellitus and hypertension and fetal causes such as infection, immune hemolytic diseases, cord accidents, metabolic disorders, malformations, and placental dysfunction. [1] IUFD can lead to serious maternal complications if left undelivered. Induction of labor in IUFD is more difficult than when the fetus is alive, partly because death usually occurs during the second or early third trimester of pregnancy when the cervix is unripe, and the uterus is less responsive to oxytocics. [2] The definition of IUFD varies in different nations, and in India, the corresponding gestation and weight are 28 weeks and 1000 g, respectively. [3, 4] Following IUFD, spontaneous expulsion of the dead fetus might take several weeks. Until then, retention of the dead fetus could cause emotional distress and intrauterine infection following rupture of the membranes. [5] About one in four women with a dead fetus retained for 4 or more weeks develop consumptive coagulopathy. [1] In view of these complications, medical induction is recommended, if it is considered safe. [6] Prostaglandins are useful for inducing labor in IUFD. [2] Of them, misoprostol, a prostaglandin E1 (PGE1) analogue, is preferred because of its low cost, stability at room temperature, and ease of administration. [3, 6] Mifepristone is a steroid which competes for progesterone receptors. When administered before misoprostol, mifepristone increases uterine sensitivity to prostaglandins and ripens the cervix [5].

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the cervix, allowing lower doses of misoprostol to induce expulsion of the dead fetus. It shortens the induction-delivery interval.\cite{5-7}

Majority of the previous studies on the induction of labor in women with IUFD (varied gestational age between 20 and 42 weeks) were observational studies with only a few randomized controlled trials, that too with small sample sizes. The doses of misoprostol and the route of administration also varied widely.\cite{5-11} Hence, we conducted a randomized placebo-controlled trial to compare the efficacy and safety of mifepristone plus misoprostol versus oral misoprostol alone for induction of labor in IUFD.

**Patients and Methods**

This clinical trial was conducted at the Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, India from November 2011 to September 2013. The study protocol was approved by the Institute Ethics Committee (Human studies) at JIPMER (No. SEC/2011/4/81). Patients diagnosed to have IUFD after 28 weeks of gestation (considered viable in developing and underdeveloped countries) were assessed for eligibility. Women with IUFD in a singleton pregnancy who were not in labor and had intact membranes were eligible to participate in the trial. Women with IUFD and chorioamnionitis, previous uterine surgery, placenta previa or unexplained vaginal bleeding, allergy to mifepristone and misoprostol, adrenal insufficiency, severe asthma, porphyria, major degree cephalopelvic disproportion, or hypertensive disorders of pregnancy were excluded from the trial.

Informed written consent was obtained from all participants. After thorough initial clinical assessment for eligibility, routine investigations and other necessary investigations were done as needed. Consenting women were randomly assigned to receive any of the two regimens. Block randomization with varying block size generated by a computer was used to randomize patients to the study arms. In one group, women received 200 mg oral mifepristone followed by 50 μg oral misoprostol every 4 h up to a maximum of 5 doses. In the other group, women received oral placebo (Tab. Calcium 250 mg) followed by 50 μg oral misoprostol every 4 h up to a maximum of 5 doses. The interval between mifepristone/placebo and the first dose of misoprostol was 24 h. After misoprostol administration, maternal pulse, blood pressure, temperature, uterine contractions, and systemic symptoms were monitored 4th hourly during the first stage and every 30 min during the second stage. Successful treatment was defined as delivery within 72 h of the first misoprostol dose. In case of failure of induction, other procedures such as extra-amniotic carboprost (PGF2α) or ethacridine lactate instillation, vaginal or sublingual PGE1, and oxytocin augmentation were used at the discretion of the treating unit consultant’s decision.

Women were followed up to hospital discharge, which was usually 24–48 h after the delivery. Adverse effects of the drugs such as nausea, vomiting, diarrhea, and fever, and complications of delivery such as hemorrhage and trauma were noted during intrapartum and postpartum periods. Completeness of uterine evacuation was confirmed by examination of expelled products of conception or by ultrasonogram in select cases when warranted clinically. The primary outcome measure was the induction to delivery interval. Other methods used in case of induction failure, adverse effects of drugs, complications of delivery, and complete uterine evacuation were the secondary outcome measures.

**Sample size**

Sample size was estimated assuming an expected difference of 10 h in the mean induction to delivery time between the two groups with a standard deviation (SD) of 15 h, at 5% level of significance and 80% power. The estimated sample size was 36 participants in each group.

**Statistical analysis**

We used the SPSS 19 for Windows statistical package (SPSS Inc., Chicago, Illinois, USA) for data analysis. Normally distributed continuous variables were summarized as mean ± SD and compared using independent t-test. Induction to delivery interval was not normally distributed. Hence, it was summarized as median (interquartile range) and compared using Wilcoxon rank-sum test. The number of treatment failure was compared by Fisher’s exact test. All tests were two-sided and \( P < 0.05 \) was considered statistically significant.

**Results**

During the study, 72 women with IUFD were recruited, and all of them were followed up to hospital discharge [Figure 1]. The groups were similar with respect to maternal age, gravidity, parity, body-mass index, gestational age, and fundal height. There were no significant differences in the mean initial Bishop score, duration of loss of fetal movements, and birth weight of the baby [Table 1]. Age of study participants ranged from 18 to 36 years. Out of 72 participants, four were teenage pregnancies (1 in mifepristone group, 3 in the placebo/only misoprostol group) and three

![Figure 1: CONSORT flow diagram](image-url)
women were elderly gravidae (1 in mifepristone group, 2 in the placebo group). The majority of women were in the age group of 20–24 years and most participants (40 [56%] women) were primigravidae – 21 (58%) women in mifepristone and 19 (53%) women in the placebo group.

Distribution of gestational age, mean fundal height, distribution of Bishop Score, and duration of loss of fetal movements were similar in both the groups. Majority of the patients in both the groups (>80%) presented within 5 days of loss of fetal movements. Mean birth weight was little higher in combination group but was not statistically significant with [Table 1]; (P = 0.164).

Median time to delivery following induction was 14.3 h and 16.4 h in the combination group and misoprostol group, respectively. The difference, however, was not statistically significant (P = 0.437); [Table 2]. A number of misoprostol doses required were also similar in the two groups (P = 0.465); [Table 2]. One woman in misoprostol alone group did not expel the products of conception completely. Instrumental evacuation was done for her. Three patients delivered with mifepristone alone in the combination group. However, in misoprostol group, no delivery happened before misoprostol administration. This difference was not statistically significant.

There were 5 failures (all were primigravidae) in the combination group and 7 failures (six primigravidae and one second gravida) in the misoprostol alone group (P = 0.541). Among 5 failures in the combination group, 2 women delivered in 73rd h, one in 85th h without any further intervention. One woman delivered with extra-amniotic PGF2a with vaginal PGE1 in 89th h, and the remaining one delivered with extra-amniotic ethacridine lactate in 94th h.

Among the 7 failures in misoprostol alone group, 2 delivered at the 84th and 89th h without any further intervention, two delivered with extra-amniotic PGF2a 73rd and 76th h, 2 needed additional PGE1 along with extra-amniotic PGF2a delivered at the 80th and 211th h, and the remaining patient was managed with extra-amniotic ethacridine lactate and delivered at the 160th h. No drug-related adverse effects were noted in both trial arms.

### Table 1: Clinical characteristics of randomized patients

| Characteristic | Combination group (n=36) | Misoprostol only group (n=38) | P |
|---------------|-------------------------|-------------------------------|---|
| Age, years    | 24.8±4.2                | 23.7±4.2                      | 0.241 |
| Gravida, n (%)| 21 (58)                 | 19 (53)                       | 0.732 |
| Multi         | 15 (42)                 | 17 (47)                       |    |
| Parity, n (%) |                         |                               |    |
| Nullipara     | 23 (64)                 | 20 (56)                       | 0.673 |
| Multipara     | 13 (36)                 | 16 (44)                       |    |
| BMI, kg/m²    | 24.04±3.57              | 23.76±3.18                    | 0.724 |
| Period of gestation, weeks | 34±4                  | 33±4                          | 0.555 |
| Birth weight of the baby, kg | 1.84±0.87             | 1.57±0.74                     | 0.164 |

Data presented as mean±SD unless indicated. SD=Standard deviation, BMI=Body mass index

### Table 2: Comparison of induction-delivery interval and number of misoprostol doses between trial arms

| Outcome variable | Combination group (n=36), n (%) | Misoprostol only group (n=38), n (%) | P |
|------------------|--------------------------------|-------------------------------------|---|
| Induction to delivery interval, h |                         |                                     |    |
| Median (IQR)     | 14.3 (8.5-33.4)            | 16.4 (10.3-32.0)                  | 0.437* |
| Number of misoprostol doses required |                         |                                     |    |
| Median (IQR)     | 3.5 (2-5)                  | 4 (3-5)                            | 0.465* |

*P value is for comparison of medians. IQR=Interquartile range

### DISCUSSION

In this trial, both regimens were well tolerated, and it appears that the combination regimen is marginally more efficacious with shorter induction to delivery times and comparatively fewer failures. However, the differences were not statistically significant.

In an observational study after 24 weeks of gestation with 200 mg oral mifepristone and 200/100 mcg of vaginal misoprostol, Wagaarachchi et al. concluded that combination method was safe and effective when compared to either of the drugs used alone.[5] In 2005, Fairley et al. reported that after 24 weeks of gestation while combination (oral mifepristone 200 mg plus vaginal misoprostol 400 micrograms up to four doses) regimen was effective, oral misoprostol administration had a higher incidence of gastrointestinal side effects.[7]
In 2006, Ranganath and Shankaregowda (Unpublished data) performed an observational study after 24 weeks of gestation with dosages similar to Wagaarachchi et al. and concluded that combination of mifepristone and misoprostol regimen was more effective and safe to induce labor in late IUFD with fewer side effects and need for less intense monitoring.\[8\]

In 2007, Väyrynen et al. in their study from 21 to 42 weeks of gestation found similar safety and efficacy for the combination (200 mg of oral mifepristone followed by a low dose 25 mcg of vaginal misoprostol) and 100 mcg vaginal misoprostol only group. However, pretreatment with mifepristone reduced the induction to delivery interval.\[9\] Sharma et al. found that combination of 200 mg of oral mifepristone and 100/50 mcg (<37 weeks/more than 37 weeks, respectively) misoprostol was more effective than the same dose of misoprostol given alone in women with IUFD after 28 weeks, and the number of doses required was less in the combination group.\[10\] In 2013, Praveena et al. found in a randomized trial (20–42 weeks of gestation) that the combination of 200 mcg oral mifepristone and 200/50 mcg vaginal misoprostol in intermediate and late IUFD, had a shorter induction to delivery interval and a lesser requirement for misoprostol doses when compared to misoprostol only group.\[11\]

In the present study, mean induction-delivery interval in both the groups was higher when compared to other studies. This might be due to the lower dose of misoprostol (50 µg) used for all gestational ages more than 28 weeks. The interval between administrations of mifepristone to misoprostol was 24 h in our trial, which is less compared to the majority of the other studies. However, with this low-dose misoprostol regimen was well tolerated, and there were no adverse effects noted in both groups.

The strengths of the present study are – this was a randomized placebo-controlled trial; there were no dropouts; and we evaluated a lower dose of oral misoprostol to minimize the adverse effects. The cervical status (Bishop Score) was not reassessed 24 h after intake of mifepristone/placebo in this trial. This could be a limitation. This would help to assess the action of mifepristone on the cervix. A larger sample size is required to study better the complications and adverse effects.

**Conclusions**

Addition of mifepristone to appears to be more effective than misoprostol alone for induction of labor in intermediate and late IUFD, although the differences were not statistically significant. A larger clinical trial is needed to define the management of IUFD.

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**Conflicts of interest**

There are no conflicts of interest.

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