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Original article

Comparing Mifepristone with Misoprostol combination to Misoprostol alone for labour induction in antepartum stillbirth

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Abstract

Background: Despite the advancement in thanatological research, stillbirth remains one of the most proscribed and misunderstood types of losses. Aim of our study was to compare the efficacy and safety of the combination of mifepristone and Misoprostol vs. Misoprostol alone for the induction of labor in antepartum stillbirth.

Methods: This study recruited fifty-two pregnant individuals at a gestational age beyond 28 weeks who had been diagnosed with antepartum stillbirth. Participants allocated to group I received an oral dose of 200 mg of Mifepristone. Subsequently, after a 24-hour interval, patients were administered 50 mcg of Misoprostol orally every 4 hours, up to a maximum of four doses. In contrast, participants in group II were provided with a placebo of Tablet Calcium (500mg). Following the same 24-hour interval, they received a dose of 50 mcg of Misoprostol orally every 4 hours, for a maximum of four doses.

Results: The mean (standard deviation) induction-to-delivery interval (IDI) in group I and group II were 8.6 (1.9) and 11.9 (3.7) hours, respectively ($p < 0.001$). In group I, the mean (SD) total dosage of Misoprostol was 65.4 (30.9) milligrams, whereas in group II, it was 126.9 (45.2) milligrams. A significant difference was observed between the two groups in terms of the total dosage of Misoprostol ($p < 0.001$).

Conclusion: These results underscore the potential benefits of Mifepristone and Misoprostol in improving outcomes for individuals experiencing antepartum stillbirth. Further research is warranted to validate and expand upon these findings, with the ultimate goal of enhancing care and support for those affected by stillbirth.

Keywords: Mifepristone, Misoprostol, Stillbirth

Introduction

Despite progress in thanatological research, stillbirth persists as one of the most formidable and enigmatic forms of loss. Its occurrence poses significant distress for caregivers and inflicts trauma upon affected families. Despite strides in medical understanding, diagnostic technologies, and therapeutic interventions, stillbirth rates remain unacceptably high, particularly in developing nations (1). The terminologies "fetal death," "fetal demise," "stillbirth," and "stillborn" collectively denote the delivery of a fetus exhibiting no signs of life. Various countries employ distinct definitions of stillbirth. According to US federal guidelines, stillbirth is delineated as fetal deaths wherein the birth weight measures 350 grams or greater. Alternatively, in instances where the weight is unspecified, the definition extends to pregnancies of 20 completed weeks gestation or beyond, calculated from the date of the last normal menstrual period (2). As per the World Health Organization's International Classification of Diseases (WHO/ICD), stillbirths are characterized by the demise of a fetus achieving a birth weight of 500 grams. Alternatively, in cases where birth weight data is absent, this definition extends to a gestational age of 22 weeks or a crown-to-heel length of 25 centimeters. To facilitate international comparisons and reporting, the WHO advocates adopting the higher threshold (1000 grams/28 weeks/35 centimeters) for categorizing third-trimester stillbirths (3,4). The American College of Obstetricians and Gynecologists (ACOG) delineates stillbirth as the

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birth of a fetus devoid of vital signs, manifesting as the absence of respiratory efforts, cardiac activity, umbilical cord pulsations, and voluntary muscle activity. Furthermore, ACOG advocates for the reporting of fetal demises occurring at 20 weeks of gestation or beyond (if gestational age is ascertainable), or with a weight equal to or exceeding 350 grams in cases where gestational age is indeterminable (5). In the United Kingdom, stillbirth is defined as the cessation of fetal life occurring at 24 weeks or more of completed gestation (6). Stillbirth is classified according to its temporal occurrence, underlying causes, and potential preventative measures, distinguishing between deaths preceding the onset of labor (antepartum) and those transpiring during labor and delivery (intrapartum). The majority of intrapartum stillbirths are attributed to suboptimal obstetric care during the birthing process. Improvements in intrapartum care, including fetal monitoring and increased availability of operative delivery, have played a significant role in mitigating the incidence of such fatalities (7).

The principal aetiologies associated with stillbirth encompass placental abruption, congenital anomalies, infections, and umbilical cord abnormalities, including entanglement or compression, leading to compromised oxygen supply to the developing fetus. Additional significant contributors to stillbirths involve conditions such as preeclampsia and medical comorbidities like diabetes. Following fetal demise, management options include either awaiting the onset of spontaneous labor or electively initiating labor induction. It is observed that a substantial proportion, approximately 80-90%, of patients undergo spontaneous labor within a fortnight subsequent to fetal demise (8,9). In instances where expectant management is chosen, apart from the psychological distress experienced by the mother, clinical considerations encompass the potential development of disseminated intravascular coagulation, which carries inherent risks of haemorrhage and additional complications such as infection, septicaemia, and maternal mortality. Consequently, there arises a necessity for labor induction. The optimal pharmaceutical agent for terminating pregnancy in cases of antepartum stillbirth must not only exhibit efficacy and safety but also be economically accessible to mitigate further financial burdens stemming from a nonviable pregnancy. Surgical methods of induction, such as membrane stripping and amniotomy, are contraindicated in the context of antepartum stillbirth due to their potential to precipitate infection. The conventional method of labor induction employing oxytocin is often associated with discomfort and reduced efficacy, given the diminished uterine sensitivity to oxytocin prior to term. A combination regimen involving Mifepristone and a prostaglandin preparation emerges as a preferred first-line intervention for labor induction in antepartum stillbirth, an approach endorsed by the National Institute for Health and Care Excellence (NICE) guidelines, particularly for late-stage antepartum stillbirth. The World Health Organization (WHO) recommends the use of oral or vaginal Misoprostol for labor induction in the third trimester of pregnancy, particularly in cases involving a nonviable or anomalous fetus (10).

Prostaglandins, notably Misoprostol, have been extensively employed for labor induction in instances of antepartum stillbirth (11). Misoprostol, an analog of prostaglandin E1, functions to stimulate uterine contractions and facilitate cervical ripening. Potential adverse effects associated with its use comprise uterine hyperstimulation and the risk of uterine rupture (12,13). Mifepristone, a steroid compound, operates through the antagonism of progesterone at the receptor level. Its mechanism involves augmentation of uterine activity, facilitation of cervical ripening, and enhancement of myometrial responsiveness to Misoprostol when administered prior to Misoprostol (13).

Adverse effects may encompass abdominal discomfort, vaginal spotting, and cramping (14). Additionally, less frequent adverse effects such as nausea, vomiting, dizziness, diarrhea, fever, and fatigue were noted. Numerous therapeutic approaches for terminating pregnancies resulting from antepartum stillbirth have been suggested, yet identifying an optimal strategy for labor induction remains a challenge. The objective of our investigation is to assess and contrast the effectiveness and safety profiles of combining Mifepristone with Misoprostol versus employing Misoprostol alone for labor induction in cases of antepartum stillbirth.

Materials & Methods

This prospective randomized controlled study was conducted subsequent to approval from the institutional ethics committee (IEC-DDUH/upn10/2021-03-15/10/v1). Eligible participants were pregnant women with a gestational period exceeding 28 weeks,

diagnosed with antepartum stillbirth as confirmed by ultrasound (absence of fetal heart pulsations). Exclusion criteria encompassed women in active labor, those with multiple pregnancies, significant cephalopelvic disproportion, a history of previous cesarean section, and medical conditions such as cardiovascular diseases, hypertensive disorders of pregnancy, thyroid disorders, grand multiparity (parity greater than or equal to 4), and antepartum hemorrhage.

Sample size determination was based on a prior study by Sharma D et al., (15) with considerations for a 95% power and 95% confidence interval, resulting in a proposed sample size of 26 participants per group (total = 52).

All eligible patients were enrolled in the study after obtaining written informed consent. Detailed medical histories were obtained, and comprehensive physical, systemic, and obstetric examinations were conducted. Routine investigations, including hemoglobin levels, blood group and Rh factor, thyroid stimulating hormone (TSH) levels, HIV, HBs Ag, VDRL, random blood sugar, coagulation profile, liver function tests, and ultrasonography, were performed. Randomization into a 1:1 ratio was achieved using a computer-generated random-number table, dividing patients into two groups. Participants in Group I were administered 200 mg of Mifepristone orally, followed by a 24-hour interval before receiving 50 mcg of Misoprostol orally every 4 hours for a maximum of 4 doses. Group II (Misoprostol group) received a placebo of T. Calcium (500mg) and underwent a similar dosing regimen of Misoprostol. Following each dose of Misoprostol, patients were closely monitored for vital signs, uterine contractions, systemic symptoms, and underwent hourly pulse checks and vaginal examinations every 4 hours. If labor failed to commence within 24 hours following the initial dose of Misoprostol, it was considered as induction failure, and subsequent management was in accordance with the hospital's protocol.

The following outcomes were recorded: the induction-to-delivery interval (defined as the duration from the administration of the first dose of Misoprostol to the complete delivery of the fetus and placenta in hours), the number of Misoprostol doses required for induction, the necessity for additional interventions such as oxytocin, and any adverse drug reactions including nausea, vomiting, diarrhea, fever, as well as complications such as retained placenta, post-partum hemorrhage, and sepsis.

Descriptive statistics were employed to present the data, with means and standard deviations utilized for continuous variables, and frequencies and percentages for categorical variables. Group comparisons were conducted using t-tests or Mann-Whitney U tests for normally or non-normally distributed continuous data, respectively, and the chi-square test for categorical variables.

Receiver Operating Characteristic (ROC) analysis was performed to assess the diagnostic performance of various biomarkers. Data were coded and recorded using MS Excel Software, and statistical analysis was carried out using Statistical Package for Social Sciences (SPSS) version 21.0. A significance level of $p<0.05$ was adopted for determining statistical significance.

Results

A total of 52 women were enrolled in the study, with observations and recordings of pertinent outcomes conducted. The mean (SD) induction-to-delivery interval (IDI) in Mifepristone with Misoprostol group was 8.6 (1.9) hours, while in Misoprostol group, it was 11.9 (3.7) hours. A significant difference in IDI between the two groups was evident ($W=140.000$, $p<0.001$).

Regarding the total dose of Misoprostol administered, the mean (SD) in Mifepristone with Misoprostol group was 65.4 (30.9) milligrams, whereas in Misoprostol group, it was 126.9 (45.2) micrograms. A notable disparity in total Misoprostol dosage between the groups was observed ($W=97.000$, $p < 0.001$).

In Mifepristone with Misoprostol group, 76.9% of participants required a single dose of misoprostol, while 17.7% required two doses. Conversely, in Misoprostol group, 11.5% received one dose, 38.5% received two doses, 34.6% received three doses, and 15.4% received four doses. A larger proportion of patients in Mifepristone with Misoprostol group required only one dose, whereas a larger proportion in Misoprostol group required two or three doses of misoprostol.

Oxytocin was needed by 23.1% of participants in Mifepristone with Misoprostol and 30.8% in

Misoprostol group, with no significant difference in the distribution of oxytocin use observed between the groups.

Side effects were experienced by 26.9% of participants in Mifepristone with Misoprostol group and 46.2% in Group 2. However, no significant difference in the overall distribution of side effects, including nausea, vomiting, cramps, diarrhea, and fever, was found between the groups ($\chi 2$ = 2.073, p=0.150).

Table 1. Comparing Mifepristone with misoprostol combination to misoprostol alone for labour induction in antepartum stillbirth.

	Mifepristone with Misoprostol group N=26 Mean (SD)	**Misoprostol group N=26 Mean (SD)**	**p-value**
IDI* (hr)	8.6 (1.9)	11.9 (3.7)	<0.001
Total Misoprostol (mcg)	65.4 (30.9)	126.9 (45.2)	<0.001
Dose No. of Misoprostol, n (%)			<0.001
1	20 (76.9)	3 (11.5)	
>1	6 (4.6)	23 (88.5)	
Oxytocin Used, n (%)			0.532
Yes	6 (23.1%)	8 (30.8%)	
No	20 (76.9%)	18 (69.2%)	
Side Effect, n (%)			0.150
Yes	7 (26.9%)	12 (46.2%)	
No	19 (73.1)	14 (53.8)	

*IDI: Induction-to-delivery interval

Discussion

The findings of this study indicate a notable disparity in the induction-to-delivery interval (IDI) between Mifepristone with Misoprostol and Misoprostol group. Specifically, participants in Mifepristone with Misoprostol, who received the combination of Mifepristone and misoprostol, exhibited a substantially shorter IDI compared to those in Misoprostol group, who received misoprostol alone. The statistically significant difference in IDI between the two groups (p<0.001) suggests that the combination therapy may offer a more efficient induction of labor in cases of antepartum stillbirth compared to misoprostol monotherapy.

Our study findings align with previous research conducted by Wagaarachchi et al (16) where the mean induction-to-delivery interval utilizing the combination of Mifepristone and misoprostol was reported as 8.5 hours, compared to misoprostol alone. Similarly, Vayrynen et al (17) reported comparable safety and efficacy between the combination therapy and misoprostol monotherapy; however, pretreatment with Mifepristone resulted in a reduction in the induction-to-delivery interval, consistent with our study findings. Chaudhuri et al (18) conducted a randomized double-blind placebo-controlled parallel group superiority trial involving 110 women who had experienced fetal demise at or beyond 20 weeks of gestation. Their study revealed a significantly shorter mean induction-to-delivery interval when utilizing Mifepristone in combination with misoprostol compared to misoprostol alone (9.8 hours and 5.7 hours, respectively).

A shorter IDI can have clinical implications, as it may reduce the duration of fetal exposure to intrauterine demise and decrease the risk of complications associated with prolonged labor, such as maternal infections and fetal distress. Therefore, these results support the notion that combining mifepristone with misoprostol could potentially improve obstetric outcomes in cases of antepartum stillbirth by expediting the delivery process.

However, it is important to interpret these findings in the context of the study's limitations, such as its sample size and potential confounding variables. Further research with larger sample sizes and controlled confounding factors is warranted to validate these results and elucidate the underlying mechanisms contributing to the observed differences in IDI between the two treatment groups. Additionally, long-term follow-up studies are needed to assess the impact of induction methods on maternal and neonatal outcomes beyond the immediate delivery period.

The mean dosage of misoprostol required for labor induction in cases of antepartum stillbirth was 65.4 micrograms in Mifepristone with Misoprostol group, whereas it was 126.9 micrograms in Misoprostol group, indicating a reduced dosage requirement when combined with Mifepristone. A higher proportion of patients in Mifepristone with Misoprostol group necessitated only a single dose of misoprostol, whereas a larger proportion in Misoprostol group required two or three doses. Comparable findings were reported in a study by Sharma D et al (15), which investigated the efficacy and safety of combining Mifepristone with

Misoprostol versus using misoprostol alone for managing antepartum stillbirth. The mean number of misoprostol doses required in Mifepristone with Misoprostol group and Misoprostol group was 1.6 (0.92) and 3 (0.95), respectively, corroborating our results. Similar outcomes were also documented by Vayrynen et al (17), who observed a reduced need for misoprostol doses in the group pretreated with Mifepristone.

Fairley et al (19) concluded that the combination method was both safe and effective, while oral misoprostol administration was associated with a higher incidence of gastrointestinal side effects. In our study, 26.9% of participants in Mifepristone with Misoprostol group experienced side effects, compared to 46.2% in Misoprostol group; however, the difference in side effects between the groups was not statistically significant overall or individually.

Our study has certain limitations first, the study was conducted at a single institution, which may limit the generalizability of the findings to other settings and populations. Second, due to the nature of the intervention (oral administration of Mifepristone and misoprostol), blinding of participants and researchers was not feasible, potentially introducing bias into the study. Third, despite randomization, there may still be inherent differences between the groups that could influence the study outcomes. Fourth, the study primarily focused on short-term outcomes related to labor induction and immediate postpartum complications, with limited assessment of long-term maternal and neonatal outcomes.

Conclusion

These findings suggest that the combination therapy of Mifepristone and Misoprostol may offer advantages in terms of efficacy and dosage requirement for labor induction in antepartum stillbirth, with comparable safety profiles to Misoprostol monotherapy. Further research with larger sample sizes and longer follow-up periods is warranted to validate these findings and determine the optimal induction method for improving obstetric outcomes in cases of antepartum stillbirth.

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Conflicts of Interest

The authors declare that no conflict of interest.

References

1. Lawn JE, Gravett MG, Nunes TM, Rubens CE, Stanton C. Global report on preterm birth and stillbirth (1 of 7): definitions, description of the burden and opportunities to improve data. BMC pregnancy and childbirth. 2010 Feb;10(1):1-22.
2. National Center for Health Statistics (US). State definitions and reporting requirements for live births, fetal deaths, and induced terminations of pregnancy. US Department of Health and Human Services, Public Health Service, Office of Health Research, Statistics and Technology, National Center for Health Statistics; 1981
3. Neonatal WH, Mortality P. Country, regional and global estimates. Geneva, Switzerland: World Health Organization. 2006.
4. Zieman M, Fong SK, Benowitz NL, Banskter D, Darney PD. Absorption kinetics of Misoprostol with oral or vaginal administration. Obstet Gynecol 1997; 90(1): 88-92.
5. American College of Obstetricians and Gynecologists. Management of stillbirth. ACOG practice bulletin no 102. Obstet Gynecol 2009; 113(3): 748-61.
6. Dellicour S, Bhange S, Tila M, et al. Brighton Collaboration Stillbirth Working Group. Stillbirth: Case definition and guidelines for data collection, analysis, and presentation of maternal immunization safety data. Vaccine. 2016; 34(49): 6057-6068.
7. Rohde LE, Clausell N, Ribeiro JP, et al. Health outcomes in decompensated congestive heart failure: a comparison of tertiary hospitals in Brazil and United States. Int j cardiol 2005; 102(1): 71-7.
8. Stillbirth Collaborative Research Network Writing Group. Causes of death among stillbirths. Jama 2011; 306(22): 2459-68.
9. Maheshwari S, Borgohain D. Methods of induction of labor in intrauterine fetal demise: A comparative

study. Int J Repro Contraception Obstet Gynecol 2017; 6(9): 3911-5.
10. Tsakiridis I, Mamopoulos A, Athanasiadis A, Dagklis T. Induction of labor: an overview of guidelines. Obstet gynecol survey 2020; 75(1): 61-72.
11. Bugalho A, Bique C, Machungo F, Faúndes A. Induction of labor with intravaginal misoprostol in intrauterine fetal death. Am J Obstet Gynecol 1994; 171(2): 538- 41.
12. Hofmeyr GJ, Gülmezoglu AM, Pileggi C. Vaginal misoprostol for cervical ripening and induction of labour. Cochrane Database Syst Rev 2010; 2010(10): CD000941.
13. Stitely ML, Browning J, Fowler M, Gendron RT, Gherman RB. Outpatient cervical ripening with intravaginal misoprostol. Obstet Gynecol 2000; 96(5 Pt 1): 684-8.
14. Larsson PG, Platz-Christensen JJ, Thejls H, Forsum U, Påhlson C. Incidence of pelvic inflammatory disease after first-trimester legal abortion in women with bacterial vaginosis after treatment with metronidazole: a double-blind, randomized study. Am J Obstet Gynecol 1992; 166(1): 100-3.
15. Sharma D, Singhal SR, Poonam, Paul A, Kunika. Comparison of Mifepristone combination with misoprostol and misoprostol alone in the management of intrauterine death: condensation - misoprostol and Mifepristone combination is more effective than misoprostol alone in the management of intrauterine death. Taiwan J Obstet Gynecol 2011; 50(3): 322-5.
16. Wagaarachchi PT, Ashok PW, Narvekar NN, Smith NC, Templeton A. Medical management of late intrauterine death using a combination of mifepristone and misoprostol. BJOG: Int J obstet Gynecol. 2002 Apr 1;109(4):443-7.
17. Vayrynen W, Heikinheimo O, Nuutila M. Misoprostol-only versus mifepristone plus misoprostol in induction of labor following intrauterine fetal death. Acta Obstet Gynecol Scand 2007; 86(6): 701-5.
18. Chaudhuri P, Datta S. Mifepristone and misoprostol compared with misoprostol alone for induction of labor in intrauterine fetal death: A randomized trial. J Obstet Gynaecol Res 2015 Dec; 41(12): 1884-90.
19. Fairley TE, Mackenzie M, Owen P, Mackenzie F. Management of late intrauterine death using a combination of mifepristone and misoprostol—experience of two regimens. Eur J Obstet Gynecol Reprod Biol 2005; 118(1): 28-31.