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Comparison of Combined Mifepristone and Misoprostol Therapy with Misoprostol Alone in Medical Termination of Intrauterine Fetal Demise

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Abstract

Medical termination of intrauterine feat demise (IUFD) seeks effective uterine evacuation with minimal complications. Since misoprostol alone is commonly used, mifepristone pretreatment may improve efficacy; however, comparative evidence in Bangladesh is very limited. A cross-sectional, comparative study was conducted in the Department of Obstetrics & Gynaecology of Community Based Medical College, Bangladesh (CBMC,B) Hospital, Mymensingh, Bangladesh, between January and December of 2023, to compare the efficacy and safety of combined mifepristone and misoprostol therapy with misoprostol alone for medical termination of IUFD. A total of 80 women with confirmed IUFD were purposively allocated in two groups having 40 in each group – group A received mifepristone followed by misoprostol, while group B received only misoprostol. Primary outcomes were induction-to-expulsion interval and complete expulsion rate; while secondary outcomes included total misoprostol dose and maternal complications. The induction-to-expulsion interval was much lower in group A compared to group B (14.2±3.6 hours vs. 22.8±5.1 hours; p<0.001). Regarding treatment success, complete expulsion within 24 hours was achieved much more in group A compared to group B (92.5% vs. 72.5%; p<0.05). The total dose of misoprostol required was significantly lower in group A as doses of ≤600 µg were sufficient in 65.0% of women receiving mifepristone pretreatment, whereas 62.5% of women in the misoprostol alone group (group B) required ≥800 µg (p<0.05). Adverse effects such as fever, nausea/vomiting and excessive bleeding were observed in both groups. However, the overall incidence of adverse effects was comparable and no statistically significant differences were observed (p>0.05). Combined therapy with mifepristone and misoprostol are more effective than using only misoprostol for termination of IUFD offering shorter induction time and higher success rate without increasing maternal risk.

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Introduction

Intrauterine fetal demise (IUFD) is a distressing obstetric complication defined as fetal death occurring after the age of viability and before the onset of labour.[1] Globally, IUFD remains a significant contributor to perinatal mortality, with higher prevalence reported in low- and middle-income countries due to limited antenatal surveillance, maternal comorbidities, and delayed access to healthcare facilities.[2] Beyond its medical implications, IUFD imposes profound psychological and emotional burdens on affected women and families, making timely and safe termination of pregnancy a crucial component of care.[3] Once IUFD is diagnosed, expeditious uterine evacuation is generally recommended to prevent complications such as disseminated intravascular coagulation, infection, prolonged hospitalization, and emotional distress.[4]

Medical termination using pharmacological agents has largely replaced surgical methods in many settings due to its non-invasive nature, cost-effectiveness, and lower requirement for specialized

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surgical expertise.[5] Among these agents, misoprostol, a synthetic prostaglandin E1 analogue, is widely used because of its uterotonic properties, stability at room temperature, and multiple routes of administration.[6] Despite its widespread use, misoprostol alone is often associated with prolonged induction-to-expulsion intervals, higher cumulative doses, and variable success rates, particularly in later gestations or in women with an unfavorable cervix.[4,7] These limitations have prompted exploration of combination regimens to improve efficacy and patient outcomes. Mifepristone, an antiprogestin, acts by blocking progesterone receptors, leading to cervical softening, increased uterine contractility, and enhanced sensitivity to prostaglandins.[8] Pretreatment with mifepristone has been shown to prime the uterus, thereby reducing the dose and duration of misoprostol required for successful termination.[9] Evidence showed that the combined use of mifepristone and misoprostol is superior to misoprostol alone in terms of shorter induction times, higher complete expulsion rates, and reduced need for additional interventions in cases of IUFD and second-trimester termination.[10-12] However, in Bangladesh, misoprostol alone remains the more commonly used agent for medical termination of IUFD due to availability, cost considerations, and limited local evidence supporting combination therapy. Therefore, the present study was designed to compare combined mifepristone and misoprostol therapy with misoprostol alone for medical termination of IUFD in a community based hospital in Bangladesh.

Methods

This cross-sectional, comparative study was conducted in the Department of Obstetrics & Gynaecology of Community Based Medical College, Bangladesh (CBMC,B) Hospital, Mymensingh, Bangladesh, between January and December of 2023. The study population consisted of pregnant women diagnosed with intrauterine fetal demise (IUFD) who were admitted for medical termination of pregnancy during the study period. A total of 80 participants were purposively selected and allocated into two groups having 40 women in each group.

Inclusion criteria: Women with ultrasonographically confirmed intrauterine fetal demise at ≥24 weeks of gestation were included in the study. Participants were required to be hemodynamically stable, willing to undergo medical termination, and able to provide informed written consent. Both primigravida and multigravida women were eligible.

Exclusion criteria: Women with a history of hypersensitivity to mifepristone or misoprostol, previous uterine surgery including cesarean section or myomectomy, suspected uterine rupture, placenta previa, severe anemia, coagulopathy, or active pelvic infection were excluded. Patients requiring immediate surgical intervention were also excluded from the study.

Women in group A received oral mifepristone followed by misoprostol after an appropriate interval, while group B received only misoprostol according to the hospital protocol. Patients were monitored for induction-to-expulsion interval, completeness of expulsion, total misoprostol dose, and adverse effects until completion of uterine evacuation. All data was recorded in the patient data sheet.

Collected data were entered and analyzed using IBM SPSS Statistics for Windows, version 23 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean±SD (standard deviation) and

compared using Student's t-test, while categorical variables were expressed as frequency and percentage and analyzed using the chi-square test. A p-value of <0.05 was considered statistically significant. The study was approved by the Ethical Review Committee of Community Based Medical College, Bangladesh (CBMC,B), Mymensingh, Bangladesh.

Results

A total of 80 women with confirmed intrauterine fetal demise were included in the study, with 40 women in each group. The baseline sociodemographic and clinical characteristics were comparable between the two groups, and no statistically significant differences were observed in age group, gravida and mode of previous delivery (p>0.05) (Table-I). Gestational age at termination was predominantly between 29–32 weeks in both groups, accounting for 55.0% and 52.5% in group A and group B respectively. No significant difference was observed between two groups (p>0.05). The induction-to-expulsion interval much lower in group A compared to group B (14.2±3.6 hours vs. 22.8±5.1 hours; p<0.001). Regarding treatment success, complete expulsion within 24 hours was achieved much more in group A compared to group B (92.5% vs. 72.5%; p<0.05). The total dose of misoprostol required was significantly lower in group A as doses of ≤600 µg were sufficient in 65.0% of women receiving mifepristone pretreatment, whereas 62.5% of women in the misoprostol alone group (group B) required ≥800 µg (p<0.05). Adverse effects such as fever, nausea/vomiting and excessive bleeding were observed in both groups. However, the overall incidence of adverse effects was comparable and no statistically significant differences were observed (p>0.05) (Table-II).

Table-I: Baseline demographic and clinical characteristics of the study participants (N=80)

Variables	Group A (n=40)	Group B (n=40)	p-value
Age group (in years)			
≤30	18 (45.0%)	19 (47.5%)	>0.05^{NS}
>30	22 (55.0%)	21 (52.5%)	
Gravida			
Primigravida	16 (40.0%)	17 (42.5%)	>0.05^{NS}
Multigravida	24 (60.0%)	23 (57.5%)	
Mode of previous delivery			
Normal vaginal delivery	22 (55.0%)	21 (52.5%)	>0.05^{NS}
Caeserean section operation	18 (45.0%)	19 (47.5%)	

Chi-square test was applied; NS=not significant.

Table-II: Comparison of clinical effects of combined mifepristone and misoprostol therapy with misoprostol alone among study participants (N=80)

Variables	Group A (n=40)	Group B (n=40)	p-value
Gestational age (in weeks)			
25–28	14 (35.0%)	15 (37.5%)	>0.05^{NS}
29–32	22 (55.0%)	21 (52.5%)	
>32	4 (10.0%)	4 (10.0%)	
Induction-to-expulsion interval*			
Mean±SD (in hours)	14.2±3.6	22.8±5.1	<0.001^{S}
Outcome			
Complete expulsion	37 (92.5%)	29 (72.5%)	<0.05^{S}
Incomplete expulsion	3 (7.5%)	11 (27.5%)	
Amount of misoprostol required			
≤600 µg	26 (65.0%)	15 (37.5%)	<0.05^{S}
≥800 µg	14 (35.0%)	25 (62.5%)	
Adverse effects			
Fever	8 (20.0%)	9 (22.5%)	>0.05^{NS}
Nausea/vomiting	6 (15.0%)	7 (17.5%)	
Excessive bleeding	3 (7.5%)	4 (10.0%)	

*Unpaired Student's t-test and Chi-square test were applied; S=significant, NS=not significant.

Discussion

The present study compared the effectiveness and safety of combined mifepristone and misoprostol with misoprostol alone for medical termination of intrauterine fetal demise (IUFD). The findings demonstrate that pretreatment with mifepristone significantly improves induction outcomes without increasing maternal complications, supporting the growing body of evidence favoring combination regimens. In this study, baseline demographic and obstetric characteristics were comparable between the two groups, ensuring that observed differences in outcomes were attributable to the treatment protocols rather than confounding variables. Similar baseline comparability has been emphasized as a critical factor in previous comparative studies evaluating medical termination methods for IUFD.[10-12] The majority of participants were multigravida and in the mid-second trimester, reflecting the typical clinical profile of IUFD cases reported in South Asian settings.[12-14] A key finding of this study was the significantly shorter induction-to-expulsion interval in the combined mifepristone and misoprostol therapy compared to administration of only misoprostol. This observation aligns with multiple studies reporting that mifepristone priming enhances cervical ripening and uterine responsiveness to prostaglandins, thereby expediting fetal expulsion.[10-14] Shorter induction times are clinically important, as prolonged labor induction is associated with increased maternal discomfort, higher infection risk, and greater emotional distress.[15] The higher rate of complete expulsion within 24 hours observed in the combined regimen group further supports its superior efficacy. Similar success rates exceeding 90% have been reported in several previous studies evaluating combination therapy for second-trimester termination and IUFD.[11,13]

In contrast, misoprostol-alone regimens have been associated with higher rates of incomplete expulsion and need for additional interventions, including repeat dosing or surgical evacuation.[16,17] Reducing the need for such interventions is particularly relevant in resource-limited settings, where access to emergency surgical services may be constrained. Another notable finding was the significantly lower total dose of misoprostol required in the combined regimen group. This is consistent with pharmacological evidence that mifepristone increases myometrial sensitivity to prostaglandins, allowing effective termination with lower cumulative doses.[15,18,19] Lower misoprostol requirements may translate into fewer dose-related adverse effects, improved patient tolerance, and reduced drug-related costs, which is an important consideration in low- and middle-income countries such as Bangladesh. Regarding safety, the incidence of maternal side effects – including fever, gastrointestinal symptoms, and excessive bleeding – was comparable between the two groups, with no statistically significant differences. Importantly, no major complications such as uterine rupture or severe hemorrhage were observed. These findings are in agreement with previous studies reporting that combination regimens do not increase maternal morbidity compared to misoprostol alone.[11,20] This reinforces the safety profile of mifepristone pretreatment when used under appropriate clinical supervision. From a clinical perspective, the results of this study have important implications for practice. Although misoprostol alone remains widely used in Bangladesh due to its availability and familiarity, the demonstrated benefits of combination therapy suggest that incorporating mifepristone into standard IUFD management protocols could improve efficiency and patient outcomes. This study was limited by its single-center design, purposive sampling technique,

and relatively small sample size, which may restrict generalizability of the study results in whole population. Moreover, the long-term maternal outcomes and psychological effects following termination were not evaluated.

Conclusion

This study demonstrates that combined mifepristone and misoprostol is more effective than misoprostol alone for medical termination of intrauterine fetal demise. The combination regimen significantly reduces induction-to-expulsion interval and misoprostol requirement while achieving higher success rates without increasing maternal complications, supporting its use as a preferred, safe, and efficient management option in clinical practice. Combined mifepristone and misoprostol therapy should be considered as the first-line regimen for medical termination of intrauterine fetal demise. Larger multicenter studies are recommended to strengthen evidence and guide national protocol development in similar resource-limited settings.

References

1. *Jauniaux E, Alfirevic Z, Bhide AG, Belfort MA, Burton GJ, Collins SL, et al. Placenta praevia and placenta accreta: diagnosis and management: Green-top Guideline No. 27a. BJOG. 2019;126(1):e1-e48.*
2. *Lawn JE, Blencowe H, Waiswa P, Amouzou A, Mathers C, Hogan D, et al. Stillbirths: rates, risk factors, and acceleration towards 2030. Lancet. 2016;387(10018):587-603.*
3. *Mandal M, Chaudhuri A, Banerjee D, Kanrar P, Hazra SK. Impact of management protocols of intrauterine fetal death on perceived stress: a comparative study. J Scientif Soc. 2017;44(3):121-5.*
4. *World Health Organization (WHO). Abortion care guideline. Geneva: WHO; 2022.*
5. *Zhang J, Zhou K, Shan D, Luo X. Medical methods for first trimester abortion. Cochrane Database Syst Rev. 2022;5(5):CD002855.*
6. *Tang O, Ho PC. Pharmacology of Prostaglandins. In: Ledger WL, Ho PC. eds. Gynecological Drug Therapy. New York: Informa Healthcare; 2007.*
7. *Gómez Ponce de León R, Wing D, Fiala C. Misoprostol for intrauterine fetal death. Int J Gynaecol Obstet. 2007;99(Suppl 2):S190-3.*
8. *Tang O, Ho PC. Mifepristone. In: Ledger WL, Ho PC. eds. Gynecological Drug Therapy. New York: Informa Healthcare; 2007.*
9. *Macnaughton H, Nothnagle M, Early J. Mifepristone and misoprostol for early pregnancy loss and medication abortion. Am Fam Physician. 2021;103(8):473-80.*
10. *van den Berg J, Hamel CC, Snijders MP, Coppus SF, Vandenbussche FP. Mifepristone and misoprostol versus misoprostol alone for uterine evacuation after early pregnancy failure: study protocol for a randomized double blinded placebo-controlled comparison (Triple M Trial). BMC Pregnancy Childbirth. 2019;19(1):443.*
11. *Hamel CC, Snijders MPLM, Coppus SFPJ, Vandenbussche FPHA, Braat DDM, Adang EMM. Economic evaluation of a randomized controlled trial comparing mifepristone and misoprostol with misoprostol alone in the treatment of early pregnancy loss. PLoS One. 2022;17(2):e0262894.*
12. *Abbasi S, Siddiqua SF, Alam MNA, Jesmin S, Siddiqui MMR, Rahman MT. Role of combined mifepristone and misoprostol versus misoprostol alone in induction of labour in patients with intrauterine foetal death – a randomized comparison between their outcome. Anwer Khan Modern Med Coll J. 2017;8(1):50–4.*
13. *Arjunan Y, Nichanahalli KS, Pampapati V, Maurya DK, Subrahmaniyan SR. Oral misoprostol with mifepristone versus misoprostol alone for inducing labor in intrauterine fetal death: a randomized placebo-controlled trial. Int J Adv Med Health Res. 2017;4(1):23-6.*

14. *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.*

15. *Prodan N, Breisch J, Hoopmann M, Abele H, Wagner P, Kagan KO. Dosing interval between mifepristone and misoprostol in second and third trimester termination. Arch Gynecol Obstet. 2019;299(3):675-9.*

16. *Raymond EG, Harrison MS, Weaver MA. Efficacy of misoprostol alone for first-trimester medical abortion: a systematic review. Obstet Gynecol. 2019;133(1):137-47.*

17. *Karena ZV, Shah H, Vaghela H, Chauhan K, Desai PK, Chitalwala AR. Clinical utility of mifepristone: apprising the expanding horizons. Cureus. 2022;14(8):e28318.*

18. *Nascimento MI, Cunha Ade A, Oliveira SR, Nunes GG, Alvarez FS, Villas Bôas EL. Misoprostol use under routine conditions for termination of pregnancies with intrauterine fetal death. Rev Assoc Med Bras. 2013;59(4):354-9.*

19. *Dzuba IG, Castillo PW, Bousiéguez M, Lugo Hernández EM, Castañeda Vivar JJ, Sanhueza Smith P. A repeat dose of misoprostol 800 mcg following mifepristone for outpatient medical abortion at 64-70 and 71-77 days of gestation: a retrospective chart review. Contraception. 2020;102(2):104-8.*

20. *Bridwell RE, Long B, Montrief T, Gottlieb M. Post-abortion complications: a narrative review for emergency clinicians. West J Emerg Med. 2022;23(6):919-25.*