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Comparison of Effectiveness of Combined Mifepristone & Misoprostol with Misoprostol Alone in Midtrimester (20-28 Weeks) Termination of Pregnancy in Patient of Preeclampsia with Severe Features

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Abstract | **Original Research Article**

Background: Termination of pregnancy in the midtrimester (20–28 weeks) is a high-risk procedure, particularly in women with severe preeclampsia, due to increased maternal morbidity and mortality. Pharmacological induction using misoprostol is common, but pre-treatment with mifepristone may enhance efficacy and reduce induction-to-abortion intervals. Evidence on optimal regimens in preeclamptic women is limited. ***Objective:*** To compare the effectiveness, safety, and induction-to-abortion interval of combined mifepristone and misoprostol versus misoprostol alone in midtrimester termination of pregnancy among women with severe preeclampsia. ***Methods:*** A hospital-based comparative prospective study was conducted at Dhaka Medical College Hospital from July to December 2021. Eighty-four women at 20–28 weeks of gestation with severe preeclampsia requiring termination were enrolled and randomly assigned to Group A (n=42, mifepristone 200 mg orally followed by 100–400 mcg vaginal misoprostol every 3 hours) or Group B (n=42, misoprostol alone). Primary outcome was induction-to-abortion interval; secondary outcomes included number of misoprostol doses, method of termination, blood loss, adverse effects, and need for surgical intervention. Data were analyzed using SPSS v23.0; $p<0.05$ was considered significant. ***Results:*** The mean induction-to-abortion interval was significantly shorter in Group A (12.72 ± 5.33 hours) compared to Group B (15.67 ± 4.74 hours; $p=0.010$). Group A required fewer misoprostol doses (mean 2.7 ± 1.0) than Group B (3.4 ± 1.3; $p=0.007$). Spontaneous expulsion rates were high in both groups (Group A: 97.6%, Group B: 92.9%), with minimal need for MVA/D&C. Adverse effects, including fever and diarrhea, were mild and comparable between groups ($p>0.05$). ***Conclusion:*** Pre-treatment with mifepristone significantly improves the efficiency of midtrimester medical termination in women with severe preeclampsia by shortening the induction-to-abortion interval and reducing the total misoprostol requirement, without increasing adverse effects. The combination regimen is safe, effective, and clinically advantageous in this high-risk population.

Keywords: Midtrimester termination, severe preeclampsia, mifepristone, misoprostol.

INTRODUCTION

Termination of pregnancy in the midtrimester (20–28 weeks) is a complex and high-risk procedure, particularly in women with obstetric complications such as preeclampsia with severe features. Preeclampsia, a multisystem disorder characterized by hypertension, proteinuria, and end-organ dysfunction, affects 5–8% of pregnancies globally and is a leading cause of maternal and perinatal morbidity and mortality. In severe cases, continuation of pregnancy can pose significant health risks, necessitating timely termination to prevent complications such as eclampsia, stroke, placental abruption, and multi-organ failure. [1-3]

Pharmacological methods are widely used for midtrimester pregnancy termination, with misoprostol, a prostaglandin E1 analogue, being the most commonly employed agent due to its uterotonic properties and relative safety profile. Misoprostol induces uterine contractions, leading to cervical ripening and expulsion of the fetus. However, misoprostol alone may require longer induction-to-abortion intervals and may be

associated with increased side effects such as uterine hyperstimulation, fever, and gastrointestinal symptoms, particularly in high-risk populations like preeclamptic women. [4-5]

Mifepristone, a selective progesterone receptor antagonist, has been shown to enhance the efficacy of prostaglandins in inducing abortion by promoting cervical softening and increasing uterine sensitivity to prostaglandins. The combination of mifepristone followed by misoprostol has demonstrated higher success rates, reduced induction-to-abortion intervals, and lower total misoprostol requirements in the general obstetric population. [6] This regimen may be particularly advantageous in midtrimester terminations, where rapid and effective induction is critical to minimizing maternal complications.

Women with preeclampsia with severe features present unique challenges for midtrimester termination due to their heightened susceptibility to hemodynamic instability, coagulopathy, and organ dysfunction. Rapid and effective termination is essential to reduce maternal morbidity, but the optimal pharmacological regimen in this population remains under investigation. [7-8] While misoprostol alone is commonly used, emerging evidence suggests that the addition of mifepristone may improve outcomes by accelerating the process and potentially reducing adverse effects related to prolonged induction.

Several studies have compared mifepristone-misoprostol combination regimens with misoprostol-only protocols in midtrimester abortions, but most have focused on healthy women without significant comorbidities. [9] Data on preeclamptic women are limited, and the physiological changes associated with severe preeclampsia may alter the pharmacodynamics and efficacy of induction agents. Understanding the comparative effectiveness of these regimens in this high-risk group is crucial for evidence-based clinical decision-making.

OBJECTIVE

Therefore, this study aims to compare the effectiveness, safety, and induction-to-abortion intervals of combined mifepristone and misoprostol versus misoprostol alone in midtrimester termination of pregnancy among women with preeclampsia with severe features.

METHODOLOGY

A hospital-based comparative prospective study was conducted in the Department of Obstetrics and Gynecology at Dhaka Medical College Hospital over a six-month period from July 2021 to December 2021. The study population comprised women between 20 and 28 weeks of gestation diagnosed with preeclampsia with severe features, for whom termination of pregnancy was indicated to prevent maternal and fetal complications. The lower limit of 20 weeks was chosen because preeclampsia is defined as occurring after 20 weeks of gestation.

The sample size was calculated using Cochran's formula, considering a 5% level of significance, 5% precision, and a prevalence of preeclampsia of 2.8% in developing countries. This yielded a minimum sample size of 42 participants per group, resulting in a total of 84 patients. Participants were selected through purposive sampling from hospital admissions during the study period. Each participant or their guardian randomly picked a sealed envelope containing the letters A or B to assign them to one of the two groups: group A received combined mifepristone and misoprostol, while group B received misoprostol alone.

Inclusion criteria comprised women aged 20–28 weeks of gestation with preeclampsia with severe features requiring termination and who provided informed written consent. Patients with inevitable or incomplete abortion, coagulopathy, renal disease, systemic lupus erythematosus, hypersensitivity to study drugs, multiple uterine scars, placenta previa, or disseminated intravascular coagulation were excluded. Preeclampsia with severe features was defined according to ACOG guidelines, including systolic blood pressure ≥160 mmHg, diastolic blood pressure ≥110 mmHg, thrombocytopenia, elevated liver transaminases, severe right upper quadrant pain, progressive renal insufficiency, or unexplained new-onset headache.

Participants in the combination group received 200 mg of oral mifepristone, followed 24 hours later by 100–400 mcg of vaginal misoprostol every three hours until complete expulsion of the fetus and placenta. The misoprostol-only group received the same misoprostol regimen without prior mifepristone. The primary outcome measured was the induction-to-abortion interval, while secondary outcomes included total doses of drugs required, blood loss, retained products requiring surgical intervention, uterine rupture or tear, use of additional uterotonics, side effects, and need for blood transfusion.

Data were collected through active participation, structured interviews, clinical evaluation, and review of relevant laboratory investigations. All assessments were conducted according to a pre-specified follow-up schedule. Data were entered and analyzed using SPSS version 23.0. Continuous variables were summarized using mean values, while categorical variables were expressed as frequencies and percentages. Unpaired t-tests and Chi-square tests were used to compare continuous and categorical variables, respectively, with a p-value <0.05 considered statistically significant.

Ethical considerations were strictly observed. The study involved no laboratory interventions beyond routine clinical care, and no sensitive questions were asked. Participants and their guardians were fully informed that refusal to participate or withdrawal at any point would not affect their medical care. Written informed consent was obtained from all participants and their legal guardians. The study was approved by the Ethical Review Committee of Dhaka Medical College, and departmental permission was obtained prior to data collection.

RESULTS

A total of 84 women with severe preeclampsia requiring midtrimester termination of pregnancy were enrolled in the study, with 42 patients assigned to Group A (combined mifepristone and misoprostol) and 42 patients to Group B (misoprostol alone). The age distribution was comparable between the two groups, with the majority aged 21–30 years (Group A: 54.8%, Group B: 47.6%) and a mean age of 25.9 ± 6.38 years in Group A and 26.8 ± 8.23 years in Group B (p = 0.578, not significant).

Table-1: Distribution of the study patients according to age (n=84)

Age group (years)	Group A (n=42)		Group B (n=42)		P value
	n	%	n	%	
≤20	5	11.9	6	14.3	
21-30	23	54.8	20	47.6	
31-40	14	33.3	16	38.1	
Mean ± SD	25.9±6.38		26.8±8.23		0.578ns

The induction-to-abortion interval was significantly shorter in the combination group (Group A: mifepristone plus misoprostol) compared to the misoprostol-only group (Group B). In Group A, 14.6% of patients delivered within 6 hours, 48.8% within 6–12 hours, 34.1% within 12–18 hours, and 2.4% within 18–24 hours, with a mean interval of 12.72 ± 5.33 hours. In contrast, Group B had 5.1% of patients delivering within 6 hours, 20.5% within 6–12 hours, 59.0% within 12–18 hours, and 15.4% within 18–24 hours, with a mean interval of 15.67 ± 4.74 hours. The difference between the groups was statistically significant (p = 0.010), indicating that pre-treatment with mifepristone effectively shortened the induction-to-abortion interval.

Table-2: Distribution of the study patients according to Induction of Abortion Interval (n = 80)

Induction of Abortion Interval	Group A (n = 41)		Group B (n = 39)		P value
	n	(%)	n	(%)	
< 6 hours	6	14.6	2	5.1	
6–12 hours	20	48.8	8	20.5	
12–18 hours	14	34.1	23	59.0	
18–24 hours	1	2.4	6	15.4	
Mean ± SD (hours)	12.72 ± 5.33		15.67 ± 4.74		0.010*

ns = not significant

P value reached from unpaired t-test

Figure.1 shows that spontaneously was found 41(97.6%) in group A and 39(92.9%) in group B. MVA/D&C was 1(2.4%) in group A and 3(7.1%) in group B. The difference was not statistically significant (p>0.05) between two groups.

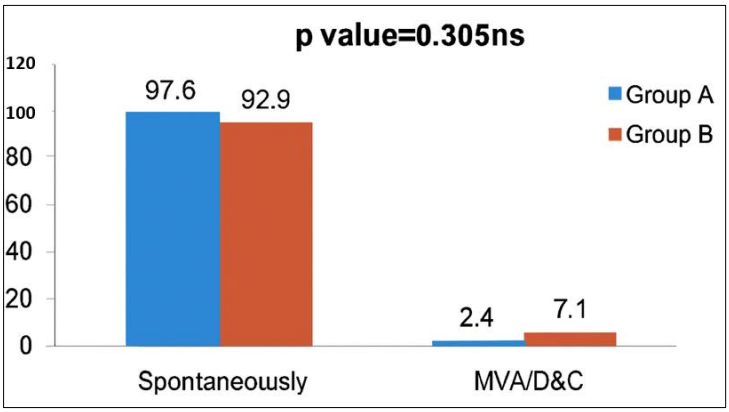

Figure 1: Distribution of the study patients according to method of termination (n=84)

Table-3: Distribution of the study patients according to blood loss (n=84)

Method of Termination	Group A (n=42)		Group B (n=42)		p value
	n	%	n	%	
Spontaneously	41	97.6%	39	92.9%	0.305
MVA/D&C	1	2.4%	3	7.1%	(ns)

The distribution of patients according to the number of misoprostol doses required showed that in Group A (mifepristone plus misoprostol), most patients needed 2 or 3 doses (18 patients each), 6 patients required 4 doses, and none required 5 doses. In contrast, Group B (misoprostol alone) had fewer patients achieving expulsion with 2 doses (7 patients), 15 required 3 doses, 14 needed 4 doses, and 6 patients required 5 doses. This demonstrates that pre-treatment with mifepristone reduced both the number of misoprostol doses and the proportion of patients needing higher doses for successful midtrimester termination.

Table-4: Number of patients according to number of doses of misoprostol required

No. of dose of misoprostol required	Group A (n=42)	Group B (n=42)
2	18	7
3	18	15
4	6	14
5	-	6

The analysis of misoprostol dosing revealed that patients in Group A (mifepristone plus misoprostol) required significantly fewer doses, with a mean of 2.7 ± 1.0, compared to 3.4 ± 1.3 doses in Group B (misoprostol alone). This difference was statistically significant (p = 0.007), indicating that pre-treatment with mifepristone effectively reduced the total number of misoprostol doses needed for midtrimester termination in patients with severe preeclampsia.

Table-5: Distribution of the study patients according to no. of dose (n=84)

	Group A (n=42)	Group B (n=42)	P value
	mean±SD	mean±SD	
No. of dosage of misoprostol required	2.7±1.0	3.4±1.3	0.007*

Among the 84 study participants, adverse effects were minimal and comparable between the two groups. In Group A (mifepristone plus misoprostol), 2.4% (1/42) experienced fever and 2.4% (1/42) experienced diarrhea. In Group B (misoprostol alone), 4.8% (2/42) reported fever and 7.1% (3/42) reported diarrhea. Statistical analysis showed no significant difference in the occurrence of fever (p = 0.556) or diarrhea (p = 0.305) between the two groups, indicating that both regimens were generally well tolerated.

Table-6: Distribution of the study patients according to adverse effects (n=84)

Adverse effects	Group A (n=42)		Group B (n=42)		P value
	n	%	n	%	
Fever	1	2.4	2	4.8	0.556^{ns}
Diarrhoea	1	2.4	3	7.1	0.305^{ns}

DISCUSSION

The present study evaluated the clinical outcomes of midtrimester termination in women with severe preeclampsia, comparing the effectiveness of combined mifepristone and misoprostol (Group A) with misoprostol alone (Group B). The demographic characteristics were comparable between the groups, with most patients aged 21–30 years and a mean age around 26 years. This age distribution aligns with other regional studies, [9] which reported that midtrimester terminations are commonly performed in young adult women due to complications such as preeclampsia, fetal anomalies, or intrauterine growth restriction. The similarity in baseline characteristics confirms that the groups were comparable, minimizing confounding effects on outcomes.

A key finding of this study was that pre-treatment with mifepristone significantly shortened the induction-to-abortion interval. The mean interval in Group A was 12.72 ± 5.33 hours, compared to 15.67 ± 4.74 hours in Group B (p = 0.010). This finding is consistent with previous research indicating that mifepristone acts by sensitizing the myometrium to prostaglandins, thereby enhancing uterine contractility and accelerating abortion. For instance, studies by Weeks *et al.,* (2012) and Ashok *et al.,* (2013) reported similar reductions in induction-to-expulsion time when mifepristone was used prior to misoprostol in second-

trimester terminations. Faster induction is particularly advantageous in women with severe preeclampsia, where prolonged exposure to pregnancy increases maternal morbidity.

The method of termination and associated blood loss were also comparable between the groups. Spontaneous expulsion occurred in over 90% of patients in both groups, with only a few requiring MVA or D&C. These findings mirror observations by Ghosh *et al.,* (2015) and ACOG (2018) guidelines, which indicate that medical termination in the midtrimester is generally effective and safe, with surgical intervention needed only in a small proportion of cases. Notably, no major hemorrhagic complications were reported, suggesting that both regimens are safe for women with preeclampsia, despite their higher baseline risk for bleeding.

Another important outcome was the number of misoprostol doses required. Patients in Group A required fewer doses (mean 2.7 ± 1.0) compared to Group B (3.4 ± 1.3), which was statistically significant ($p = 0.007$). This aligns with prior studies by Bygdeman *et al.,* (2006) and Swamy *et al.,* (2019), which showed that mifepristone pre-treatment reduces the total prostaglandin requirement, potentially lowering the risk of side effects and improving patient comfort. Furthermore, analysis of individual dose distribution demonstrated that none of the patients in Group A required 5 doses, whereas in Group B, 6 patients needed the maximum dose, highlighting the efficiency of the combination regimen.

Adverse effects were minimal and comparable between groups, with only mild fever and diarrhea reported in a few patients. No statistically significant differences were observed, indicating that both regimens are generally well tolerated. These results are consistent with other studies evaluating midtrimester medical termination, such as those by Fiala *et al.,* (2017) and Kulier *et al.,* (2011), which reported low incidences of minor gastrointestinal and febrile reactions, and no increase in severe complications associated with mifepristone pre-treatment.

Conclusion

Based on the results of this study, it can be concluded that in women with severe preeclampsia requiring midtrimester termination, the combination of mifepristone and misoprostol (Group A) is more effective than misoprostol alone (Group B). Pre-treatment with mifepristone significantly shortened the induction-to-abortion interval, reduced the total number of misoprostol doses required, and maintained a high rate of spontaneous expulsion, while adverse effects were minimal and comparable between the groups. These findings indicate that the combination regimen is both efficient and safe, providing a clinically advantageous approach for the management of midtrimester termination in high-risk preeclamptic patients.

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