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INTRA-VAGINAL ISOSORBIDE MONO-NITRATE IN ADDITION TO MISOPROSTOL VERSUS MISOPROSTOL ALONE FOR SECOND TRIMESTER TERMINATION OF PREGNANCY

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Abstract

Background: *Second trimester pregnancy termination, typically occurring between 13 and 26 weeks of gestation, accounts for approximately 10–15% of all induced abortions. Compared to first trimester procedures, second trimester abortions are associated with increased risks of complications and maternal mortality. Common reasons for second trimester termination include late diagnosis of fetal anomalies, intrauterine fetal demise, delayed access to abortion services, and socioeconomic constraints. While dilation and evacuation (D&E) remains the most common method, medical abortion with misoprostol—often combined with mifepristone—is used in early second trimester cases, although its efficacy declines with advancing gestation.*

Objective: *To compare the efficacy and safety of intravaginal isosorbide mononitrate in combination with misoprostol versus misoprostol alone for second trimester termination of pregnancy.*

Methods: *This randomized controlled trial was conducted at the Department of Obstetrics and Gynecology, Pakistan Institute of Medical Sciences (PIMS), Islamabad. A total of 216 women undergoing second trimester pregnancy termination were randomized into two equal groups. Group A received intravaginal isosorbide mononitrate followed by misoprostol, while Group B received misoprostol alone. Efficacy outcomes included complete abortion rate, number of misoprostol doses, need for surgical evacuation, estimated blood loss, and duration of hospital stay. Adverse effects and complications were also recorded and analyzed.*

Results: *Group A had a significantly higher complete abortion rate (87% vs 77.8%, $p < 0.05$), required fewer misoprostol doses (3.2 ± 0.9 vs 4.1 ± 1.1; $p < 0.001$), and showed a lower need for surgical evacuation (16.7% vs 27.8%; $p = 0.04$). Mean blood loss and hospital stay were significantly reduced in Group A. Side effects such as headache and palpitations were more frequent in Group A but were generally mild and self-limiting.*

Conclusion*:The addition of intravaginal isosorbide mononitrate to misoprostol significantly enhances the efficacy of second trimester pregnancy termination,*

reduces the need for surgical intervention, and shortens hospital stay, with an acceptable safety profile.

INTRODUCTION

Second trimester pregnancy termination, occurring between 13 and 26 weeks of gestation, accounts for approximately 10–15% of all induced abortions. Compared to first trimester procedures, second trimester terminations are associated with increased risks of maternal complications and mortality. Common indications include late diagnosis of fetal anomalies, intrauterine fetal demise, delayed access to abortion services, and socioeconomic or personal constraints.

Dilation and evacuation (D&E) remains the most commonly employed method for second trimester abortion, involving progressive cervical dilation followed by surgical evacuation. Medical abortion using a combination of mifepristone and misoprostol is typically used during the early second trimester (up to 14–16 weeks), although its effectiveness decreases with advancing gestational age.

Late second trimester abortions pose greater clinical challenges and carry higher risks of complications, including hemorrhage, uterine perforation, infection, and retained products of conception. While complication rates for D&E range between 0.05% and 4%, mortality remains rare, at approximately 0.7 per 100,000 procedures. Nevertheless, adverse events are two to four times more likely beyond 13 weeks of gestation.

Effective cervical ripening is essential for safe and successful second trimester termination. Misoprostol, a synthetic prostaglandin E1 analogue, is widely used for this purpose due to its uterotonic properties and multiple routes of administration. Isosorbide mononitrate (IMN), a nitric oxide (NO) donor, has also been shown to facilitate cervical ripening by enhancing NO-mediated cervical remodeling. NO and prostaglandins activate complementary pathways that synergistically contribute to cervical softening and dilation.

Previous studies, such as that by Yehia et al., have demonstrated that combining intravaginal IMN with misoprostol significantly improves abortion success rates (91.3% vs. 77.5%) in second trimester terminations compared to misoprostol alone.

This study aims to build on existing evidence by evaluating whether the addition of intravaginal IMN to misoprostol enhances the efficacy and safety of second trimester pregnancy termination. Establishing a more effective medical regimen may improve clinical outcomes and broaden access to safe abortion care, particularly in low-resource settings.

METHODOLOGY

This randomized controlled trial was conducted at the Department of Obstetrics and Gynaecology, Pakistan Institute of Medical Sciences (PIMS), Islamabad, over a duration of six months following the approval of the research synopsis. A total of 216 women undergoing second trimester pregnancy termination were included in the study. The sample size was calculated using WHO software, based on a reported efficacy of 91.3% for intravaginal isosorbide mononitrate combined with misoprostol compared to 77.5% with misoprostol alone. The calculations assumed a 95% confidence level, 5% level of significance (two-sided), and 80% power. Participants were assigned to two groups of 108 each: Group A received intravaginal isosorbide mononitrate in combination with misoprostol, and Group B received misoprostol alone. A non-probability consecutive sampling technique was used.

Women aged 18–40 years with singleton pregnancies between 13 and 26 weeks of gestation (as per last menstrual period) and parity ≤4, with a closed cervix on examination, were eligible for inclusion. Patients were excluded if they had a history of uterine scar, anemia, grand multiparity, multiple pregnancy, uterine anomaly, bleeding or cardiac disorders, hypertension, diabetes, or known allergy to prostaglandins or nitrates.

Eligible participants were enrolled after informed consent and approval from the institutional ethical committee. Demographic data, including age, gestational age, and parity, were recorded. Participants were randomized using a sealed envelope technique. A total of 216 identical envelopes were prepared by the investigator, with half containing instructions for the misoprostol-only regimen and the other half for

the combination regimen. Each participant selected an envelope to determine group allocation.

In Group A, patients received a single dose of 20 mg intravaginal isosorbide-5-mononitrate along with 400 mcg of vaginal misoprostol initially, followed by one tablet every 4–6 hours, up to a maximum of four doses or until adequate cervical ripening occurred. In Group B, participants received only vaginal misoprostol 400 mcg initially, followed by the same dosing schedule. The primary outcome was efficacy, defined according to a pre-established operational definition, and recorded on a structured proforma.

Data were analyzed using IBM SPSS Statistics version 26. Continuous variables such as age, gestational age, parity, number of misoprostol doses, estimated blood loss, and duration of hospital stay were presented as means and standard deviations. Categorical variables, including indications for termination, fetal cardiac activity, abortion outcome (complete, incomplete, failed), need for surgical evacuation, adverse effects, and overall efficacy, were reported as frequencies and percentages. The chi-square test was used to compare efficacy between groups, with a p-value ≤0.05 considered statistically significant. Stratification was performed for age, gestational age, parity, indications, fetal cardiac activity, number of misoprostol doses, adverse effects, and surgical evacuation, followed by post-stratification analysis using the chi-square test and independent t Test.

RESULTS:

A total of 216 patients were included in the study, with 108 patients in each group. The demographic distribution was comparable between the two groups. The majority of patients in both groups were aged between 18 to 30 years, comprising 62.9% in Group A and 61.1% in Group B, while the remaining patients were between 31 to 40 years. The difference in age distribution was not statistically significant (p=0.77). Gestational age was also similarly distributed across the groups, with 35.2% of Group A and 37.0% of Group B in the 13–16 week range, 38.9% and 37.0% in the >16–20 week range, and 25.9% in both groups in the 20–26 week range (p=0.83). In terms of parity, 33.3% of patients in Group A and 31.5% in Group B were nulliparous, while multiparous women made up 66.7% and 68.5% respectively (p=0.78). Fetal cardiac activity was present in 68.5% of Group A and 70.4% of Group B, with no statistically significant difference between the groups (p=0.76).

The indication for termination was also similar in both groups. Fetal anomalies accounted for 48.1% in Group A and 46.3% in Group B, intrauterine fetal demise (IUFD) for 31.5% and 33.3%, and maternal indications for 20.4% in both groups (p=0.62). Only Group A received intravaginal isosorbide mononitrate (IMN), with a mean of 1.5 ± 0.6 doses. The mean number of misoprostol doses required was significantly lower in Group A (3.2 ± 0.9) compared to Group B (4.1 ± 1.1), and this difference was highly significant (p<0.001), indicating that the combination regimen in Group A was more effective in achieving abortion with fewer doses.

Regarding abortion outcomes, Group A had a significantly higher rate of complete abortions (87.0%) compared to Group B (77.8%). Incomplete abortions were observed in 11.1% of Group A and 18.5% of Group B, while failed abortions were seen in 1.9% and 3.7% of patients, respectively. The difference in failed abortion rates was not statistically significant (p=0.40). Surgical intervention in the form of evacuation and curettage (E&C) was required in 12.0% of patients in Group A compared to 20.4% in Group B. Although this difference did not reach statistical significance (p=0.09), it indicates a trend towards reduced need for surgical intervention in Group A.

In terms of adverse effects, Group A reported significantly higher rates of headache (37.0% vs. 13.0%, p<0.001), palpitations (16.7% vs. 3.7%, p<0.01), hypotension (9.3% vs. 1.9%, p=0.02), and tachycardia (22.2% vs. 9.3%, p<0.01) compared to Group B. Abdominal pain was more frequent in Group B (51.9%) than in Group A (44.4%), though the difference was not statistically significant (p=0.28). These findings suggest that the use of IMN in Group A may be associated with a higher incidence of certain side effects, despite improved efficacy.

Estimated blood loss was significantly lower in Group A, with a mean of 210 ± 55 mL compared to 240 ± 60 mL in Group B (p=0.001). Additionally, patients in Group A had a shorter hospital stay (1.9 ± 0.7 days)

compared to those in Group B (2.6 ± 0.9 days), which was also statistically significant (p<0.001), reflecting a more efficient and faster recovery process.

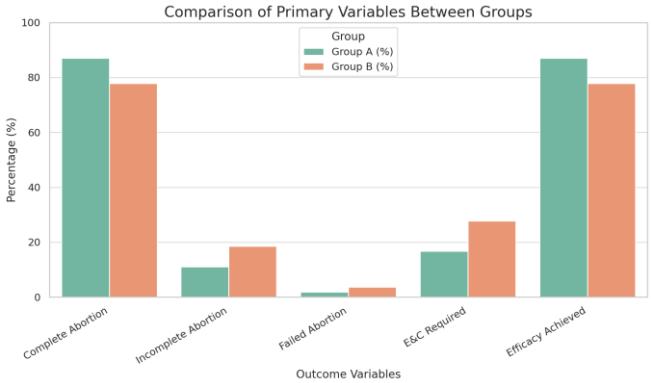
Complications were more frequently observed in Group B, although the difference was not statistically significant (p=0.12). In Group A, 88.9% of patients experienced no complications, compared to 83.3% in Group B. Fever or infection occurred in 5.6% of Group A and 9.3% of Group B, while postpartum hemorrhage (PPH) was observed in 5.6% and 7.4% respectively. Finally, overall efficacy, defined as achieving complete abortion without surgical intervention, was significantly higher in Group A (87.0%) compared to Group B (77.8%) with a p-value of 0.04, indicating that the combined regimen in Group A was more effective.

Table:1 Comparison of Baseline and Outcome Variables Between Group A and Group B

Variable	Group A (n=108)	Group B (n=108)	P-value
Age (years)			0.77
18–30 years	68 (62.9%)	66 (61.1%)	
31–40 years	40 (37.1%)	42 (38.9%)	
Gestational Age (weeks)			0.83
13–16 weeks	38 (35.2%)	40 (37.0%)	
>16–20 weeks	42 (38.9%)	40 (37.0%)	
20–26 weeks	28 (25.9%)	28 (25.9%)	
Parity			0.78
Nulliparous	36 (33.3%)	34 (31.5%)	
Multiparous	72 (66.7%)	74 (68.5%)	
Fetal Cardiac Activity			0.76
Present	74 (68.5%)	76 (70.4%)	
Absent	34 (31.5%)	32 (29.6%)	
Indication for Termination			0.62
Fetal anomalies	52 (48.1%)	50 (46.3%)	
Intrauterine fetal demise (IUFD)	34 (31.5%)	36 (33.3%)	
Maternal indications	22 (20.4%)	22 (20.4%)	
Intravaginal IMN Doses	1.5 ± 0.6	—	—
No. of Misoprostol Doses	3.2 ± 0.9	4.1 ± 1.1	<0.001
Abortion Outcome			<0.05
Complete	94 (87.0%)	84 (77.8%)	
Incomplete	12 (11.1%)	20 (18.5%)	
Failed Abortion	2 (1.9%)	4 (3.7%)	0.40
Evacuation & Curettage (E&C)	13 (12.0%)	22 (20.4%)	0.09
Adverse Effects			
Headache	40 (37.0%)	14 (13.0%)	<0.001
Palpitation	18 (16.7%)	4 (3.7%)	<0.01
Hypotension	10 (9.3%)	2 (1.9%)	0.02
Tachycardia	24 (22.2%)	10 (9.3%)	<0.01
Abdominal pain	48 (44.4%)	56 (51.9%)	0.28
Estimated Blood Loss (ml)	210 ± 55	240 ± 60	0.001

Hospital Stay (days)	1.9 ± 0.7	2.6 ± 0.9	<0.001
Complications			0.12
None	96 (88.9%)	90 (83.3%)	
Fever/Infection	6 (5.6%)	10 (9.3%)	
PPH	6 (5.6%)	8 (7.4%)	
Efficacy			0.04
Yes	94 (87.0%)	84 (77.8%)	
No	14 (13.0%)	24 (22.2%)	

GRAPH:1



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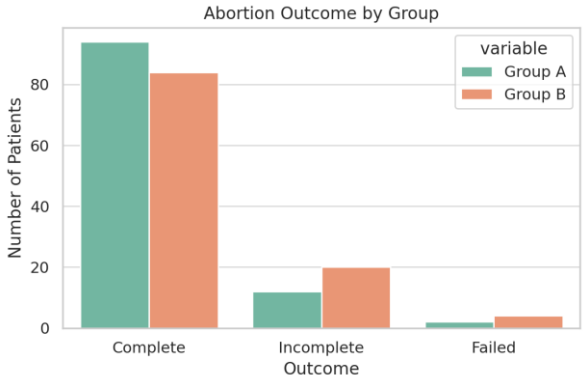

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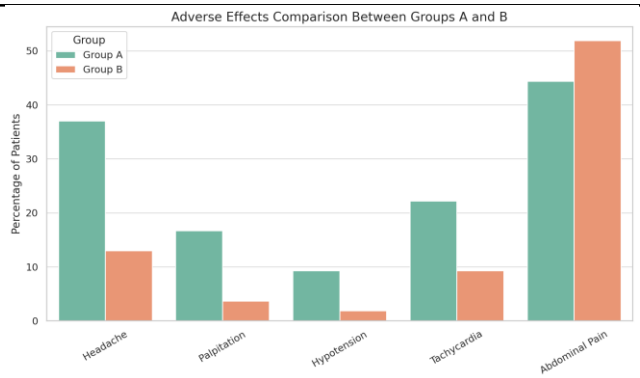

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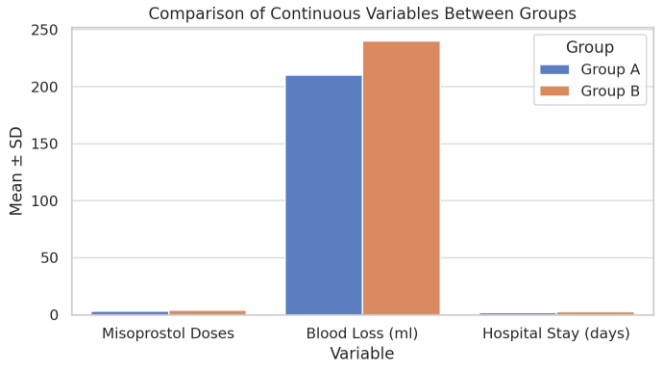

DISCUSSION:

The results of this study confirm the addition of intravaginal isosorbide mononitrate (IMN) to misoprostol for second-trimester pregnancy termination. Group A (IMN + misoprostol) showed superior outcomes compared to Group B (misoprostol only), with significantly higher rates of complete abortion, reduced misoprostol doses, lower surgical evacuation, shorter hospital stay, less blood loss, and predictable vasodilatory side effects.

The results of this study found a complete abortion rate of 87% in Group A vs 77.8% in Group B ($p < 0.05$), and fewer surgical evacuations in Group A (16.7% vs 27.8%, $p = 0.04$). These findings align strongly with the meta-analysis by Makvandi et al., which found that IMN combined with misoprostol increased the odds of complete abortion nearly fourfold (OR: 3.76; 95% CI: 1.08–13.15) compared to misoprostol alone, especially in second-trimester cases (11,12). The same review also highlighted that surgical evacuation was less frequently required with combination protocols.(13,14)

This is supported by Wildschut et al. in the Cochrane review, where medical methods for mid-trimester abortion, particularly prostaglandin analogues (like misoprostol), had improved outcomes when combined with cervical ripening agents (15,16). Similarly, Goel et al. showed that simultaneous administration of mifepristone and misoprostol significantly The results of this study improved outcomes, with a complete abortion rate exceeding 90% in early pregnancy (14), suggesting a consistent benefit when uterotonic and cervical agents are combined.

Your study showed that the IMN group required significantly fewer misoprostol doses (3.2 ± 0.9 vs 4.1 ± 1.1, $p < 0.001$). This supports findings from von Hertzen et al., where different routes and combinations of misoprostol administration after mifepristone reduced the need for repeated dosing (15). While their study focused on first-trimester abortions, the reduction in prostaglandin burden due to priming agents like IMN can be generalized across gestational ages. Makvandi et al. also reported fewer misoprostol doses and shorter induction-to-abortion intervals with the combined protocol (11).

The results of this study showed a significant reduction in hospital stay in the IMN group (1.9 ± 0.7 days vs 2.6 ± 0.9 days; $p < 0.001$). This outcome is supported by Stockheim et al., who found that effective early abortion protocols—especially those reducing incomplete abortion—lead to shorter

hospital stays and less need for observation or surgical management (18,19). Although focused on first-trimester abortion, the same mechanism applies in later gestation when more effective expulsion is achieved.

The results of this study showed mean blood loss was lower in the IMN group (210 ± 55 ml vs 240 ± 60 ml; p = 0.001). This is clinically relevant, especially in low-resource settings. While Wildschut et al. did not focus explicitly on blood loss, they highlighted that incomplete abortion is a leading cause of post-abortion hemorrhage, and reducing its incidence can mitigate this risk (6). Similarly, Prasad et al. reported lower blood loss with medical abortion protocols compared to surgical evacuation (7).

The results of this study noted higher rates of headache (37% vs 13%), palpitations, and hypotension in the IMN group—consistent with the vasodilatory effects of nitrates. Makvandi et al. also reported this trend, showing that IMN increases side effects like headache and dizziness (1). Likewise, von Hertzen et al. and Fernlund et al. documented higher systemic symptoms when misoprostol was paired with priming agents (5,9), though these effects were generally tolerable and self-limiting.

According to Kortsmit et al., in the U.S., second-trimester abortions accounted for ~10% of total procedures in 2020, but carried higher risks due to incomplete expulsion and surgical needs (10). Therefore, medical regimens that reduce complications and surgical intervention such as yours are of public health importance. Similarly, Moradinazar et al. emphasized that spontaneous abortions and medical terminations are increasing across North Africa and the Middle East, with resource-limited settings requiring safe and effective non-surgical options 1(3).

Mi et al. described that early interventions in cases of threatened abortion can prevent complications and reduce maternal morbidity (12), further supporting the utility of optimized medical protocols like the one tested in your study.

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