

Comparison of Two Misoprostol Doses for the Occurrence and Severity of Meconium-stained Liquor in Pre-labor Rupture of Membranes

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Abstract

Background: Premature rupture of membranes (PROM) and meconium-stained liquor (MSL) are important obstetric conditions and may increase the risk of neonatal complications, including meconium aspiration syndrome (MAS), necessitating timely assessment and appropriate labor management.

Objective: To compare the severity of MSL between two doses of misoprostol (25 µg vs. 50 µg) used for labor induction in patients with PROM.

Methods: This observational study was conducted from July 2024 to September 2024 at Kohi Goth Women's Hospital, Karachi, Pakistan. A total of 100 confirmed PROM women underwent labor induction either immediately or after expectant management for up to 24 hours were categorized into two groups according to the misoprostol dose received. The primary outcome was severity of MSL (Grade I–III). Secondary outcomes included mode of delivery and number of doses required.

Results: Mean age was 27.10 ± 4.10 years in the 25 µg group and 26.68 ± 4.47 years in the 50 µg group. The 50 µg group had a higher proportion of women requiring only one dose (44% vs. 30%, $p = 0.107$); however, the difference was not significant. The rate of spontaneous vaginal delivery was higher in the 25 µg group (86%) compared with 52% in the 50 µg group, where the rate of cesarean section was 48% ($p < 0.001$). There was also a significant difference in the severity of MSL ($p < 0.001$), which was considerably greater in the 50 µg group.

Conclusion: The 25 µg dosage i.e. lower-dose regimen was associated with less severe MSL and a higher proportion of spontaneous vaginal delivery in this sample.

Key words: Meconium aspiration syndrome, premature rupture, labor, maternal health, neonatal outcomes.

Introduction

The PROM is a condition that significantly influences labor management and outcomes, especially concerning neonatal and maternal health.¹ Additionally, MSL is a condition where fetal stool is present in the amniotic fluid, potentially indicating fetal distress.² It occurs in about 8-20% of deliveries and can lead to complications such as MAS, which poses significant risks to the newborn.³

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Authors Contribution

SZ conceptualized the project, did the literature search and review the draft. AAM did the data collection, performed the statistical analysis and drafting, revision & writing of manuscript.

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The management of PROM in the presence of MSL presents a specific clinical dilemma. While induction of labor is often indicated, the choice of agent and dosage must consider the potential for exacerbating fetal distress, of which MSL is a marker.^{4,5} Prostaglandins like misoprostol, while effective for cervical ripening, carry a known risk of uterine hyperstimulation,^{6,7} which could theoretically worsen fetal oxygenation in an already compromised fetus (as suggested by MSL).^{8,9} Therefore, a lower dose might mitigate this risk while still achieving induction.¹⁰

However, evidence directly comparing the impact of different misoprostol doses on MSL in PROM is scarce, especially in settings like Pakistan.¹¹⁻¹³ Local studies have highlighted MSL as a significant risk factor for adverse neonatal outcomes,^{12,13} but have not evaluated induction protocols in this context. International guidelines recommend lower doses for safety,^{7,10} but their specific effect on MSL progression remains unquantified.

PROM is a common obstetric condition that significantly influences labor management and outcomes. MSL occurs in 8-20% of deliveries and is associated with meconium aspiration syndrome and adverse neonatal outcomes. Misoprostol is widely used for labor induction in PROM, but the optimal dose to minimize MSL severity remains unclear, particularly in the Pakistani context. This study aimed to compare the severity of MSL between two misoprostol dosages (25 µg vs. 50 µg) in patients with PROM.

Hence, in the Pakistani context, determining the optimal misoprostol dose for PROM with MSL requires a nuanced approach that directly evaluates the fetal marker (MSL severity). Therefore, this study aimed to compare the severity of MSL between two misoprostol dosages (25 µg vs. 50 µg) in patients with PROM.

Methods

A prospective observational comparative study was conducted at Kohi Goth Women's Hospital in Karachi, Pakistan, from 5th July to 30th September 2024. The written informed consent was obtained from all participants prior to enrolment.

Participants were recruited through non-probability sampling, and all eligible women during the study period fulfilling the inclusion criteria and consenting to participate were recruited. The sample size was calculated using the Roasoft online Sample Size Calculator, considering a population size of 60 from a previous study,¹² a 5% margin of error, a 95% confidence interval, and a 50% response rate, resulting in a calculated sample size of 53. To account for a 10% non-response, the sample size was increased to 59. However, because all eligible participants during the study period were included, a total of 100 participants (50 per group) were ultimately analyzed; this represented a convenience sample of all eligible records meeting the inclusion criteria during the study period.

Eligibility criteria included women with a confirmed diagnosis of PROM (defined as rupture of membranes at a gestational age >37 weeks before the onset of labor),¹⁴ who were scheduled for labor induction either immediately or after a period of expectant management not exceeding 24 hours. Only singleton pregnancies with a live fetus in cephalic presentation and an unscarred uterus were

considered. Those women with clinical signs suggestive of Chorioamnionitis (maternal fever >38°C, uterine tenderness, fetal tachycardia, or purulent amniotic fluid, as per clinical judgement) at admission were also included, as expedited delivery was indicated. Co-morbid conditions such as GDM and PIH were not grounds for exclusion. Exclusion criteria were: multiple gestation, non-cephalic fetal presentation, known major fetal anomaly, uterine scar (from previous caesarean section or uterine surgery), placental abnormalities (e.g., placenta Previa), or any contraindication to vaginal delivery or prostaglandin use.

Women admitted with PROM who met the eligibility criteria were identified. Based on the standard dosage administered as per the treating physician's decision, participants were categorized into two groups: those who received 25 µg (Group 1, n=50) and those who received 50 µg (Group 2, n=50) of sublingual misoprostol for labor induction. The dose of misoprostol was selected by the treating physician based on clinical judgment, not by random assignment (Figure-1).

The information regarding participants' age, comorbidity, gravida status, duration of PROM, misoprostol dosage, and number of doses given to the patient (the total dose refers to the per-administration dose (25 µg or 50 µg) repeated every 6 hours if needed, up to two doses), MSL grade at the time of membrane rupture/amniotomy, and mode of delivery was obtained using a structured proforma. MSL was categorized clinically as Grade I (light meconium staining), Grade II (moderate staining), and Grade III (heavy meconium staining) based on visual assessment of amniotic fluid during examination,² as per institutional protocol.

Data were entered into an Excel sheet, coded, and transferred to SPSS version 26 for analysis. Normality of continuous variables was assessed using the Shapiro-Wilk test. Categorical variables were presented as frequencies and percentages, while continuous variables were presented as means and standard deviations or medians and interquartile ranges as appropriate. Baseline characteristics were compared using independent t-tests for continuous variables and Chi-square tests for categorical variables. Post-stratification associations were examined using the Chi-square test. A *p*-value of ≤0.05 was considered statistically significant.

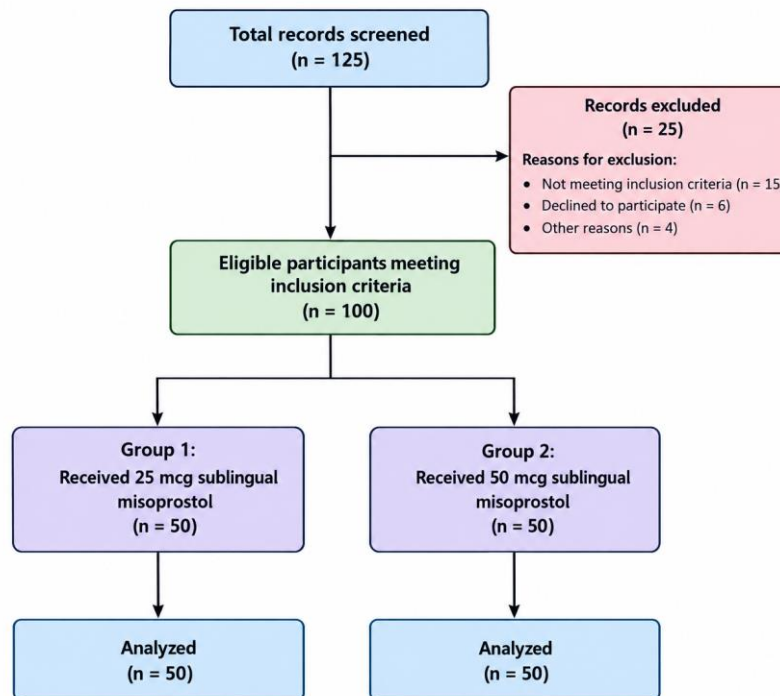


Figure 1: Participant flow diagram.

Results

The baseline characteristics of participants were comparable between groups. The mean age of the participants was 27.10 ± 4.102 years and 26.68 ± 4.465 years, receiving 25 μg and 50 μg of misoprostol, respectively. In the 50- μg group, 44% of participants required only one dose of misoprostol, compared to 30% in the 25- μg group. There was a significant difference in the mode of delivery ($p < 0.001$). The rate of spontaneous vaginal delivery was overwhelming in the 25 μg group (86%) compared with 52% in the 50 μg group, where the rate of cesarean section was 48%. Second, there was also a significant difference in the severity of MSL ($p < 0.001$). The predominant mild (56% Grade I) staining was in the 25 μg group, while the moderate (64% Grade II) staining was found more commonly in the 50 μg group (Table-1).

The relationship between the severity grade of MSL and other variables in each of the dosage groups indicated that there were no statistically significant internal relationships. The mean grade of MSLs in the 25 μg group did not vary significantly depending on the number of doses needed ($p\text{-value} = 0.216$), mode of delivery ($p\text{-value} = 0.554$), and whether the patient was primigravida or multigravida ($p\text{-value} = 0.352$). The same was the case with the 50 μg group, where the severity of MSL was not

dependent on the number of doses ($p\text{-value} = 0.814$), mode of delivery ($p\text{-value} = 0.623$), and gravida status ($p\text{-value} = 0.945$). The proportion of severe MSL was higher in the 50 μg group; however, no clinical parameters were statistically associated with MSL severity in the dosage groups. This suggests that the dosage may be associated with increased severity of MSL, independent of other clinical parameters; however, causality cannot be established due to the observational design and unadjusted confounders (Table-2).

Table-2 presents within-group analyses examining whether clinical parameters (number of doses, mode of delivery, and gravida status) are associated with the severity of MSL within each dosage group. No statistically significant associations were observed in either group, indicating that the severity of MSL was not dependent on these clinical parameters within a given dosage regimen.

Discussion

The present research showed a statistically significant association between the dosage of sublingual misoprostol used for labor induction and two key clinical outcomes: the severity of meconium-stained liquor (MSL) and the mode of delivery. The first notable finding was the difference

Table 1: Comparison of different clinical parameters among the participants receiving different dosages of misoprostol. (n=100)

Variables		Dosage 25 µg N=50(%)	Dosage 50 µg N=50(%)	p-values
Age	(years, mean ± SD)	27.10 ± 4.102	26.68 ± 4.465	0.619
Comorbidity	None	48 (96)	43 (86)	0.987
	Pregnancy-Induced Hypertension	1 (2)	4 (8)	
	Gestational Diabetes Mellitus	1 (2)	3 (6)	
Number of doses	1	15 (30)	22 (44)	0.107
	2	35 (70)	28 (56)	
Mode of delivery	Spontaneous Vaginal Delivery	43 (86)	26 (52)	0.000*
	Lower Segment Cesarean Section	7 (14)	24 (48)	
Gravida	Primigravida	23 (46)	18 (36)	0.208
	Multigravida	27 (54)	32 (64)	
Severity of MSL	Grade I	28 (56)	8 (16)	0.000*
	Grade II	16 (32)	32 (64)	
	Grade III	6 (12)	10 (20)	

*Statistically significant at <0.05 level, MSL=Meconium Stained Liquor

Table 2: Association of clinical parameters with MSL grade within each dosage group among participants. (n = 100)

Variables		Dosage 25 µg N=50(%)			p-value	Dosage 50 µg N=50(%)			p-value
		Grade I MSL	Grade II MSL	Grade III MSL		Grade I MSL	Grade II MSL	Grade III MSL	
Number of doses	1	9 (60)	6 (40)	0	0.216	4 (18.2)	13 (59.1)	5 (22.7)	0.814
	2	19 (54.3)	10 (28.6)	6 (17.1)		4 (14.3)	19 (67.8)	5 (17.9)	
Mode of delivery	SVD	23 (53.5)	15 (34.9)	5 (11.6)	0.554	5 (19.2)	15 (57.7)	6 (23.1)	0.623
	LSCS	5 (71.4)	1 (14.3)	1 (14.3)		3 (12.5)	17 (70.8)	4 (16.7)	
Gravida	PG	15 (65.2)	5 (21.7)	3 (13.0)	0.352	3 (16.7)	11 (61.1)	4 (22.2)	0.945
	MG	13 (48.1)	11 (40.7)	3 (11.1)		5 (15.6)	21 (65.7)	6 (18.7)	

SVD = Spontaneous Vaginal Delivery; LSCS = Lower Segment Cesarean Section; MSL = Meconium Stained Liquor. Values are presented as frequencies and percentages (n, %). p-values were calculated using the Chi-square test. p-value of ≤ 0.05 was considered statistically significant.

between the two groups in the distribution of MSL grades ($p < 0.001$). While the 25 µg cohort was characterized by a majority of mild, Grade I MSL (56%), the 50 µg group exhibited a shift towards moderate Grade II MSL (64%), with a higher proportion of the most severe Grade III cases (20% vs. 12%). These findings align with clinical expectations that a lower dose of misoprostol might be better tolerated and associated with fewer complications,¹⁵ though it might require additional doses for efficacy in some cases.

A previous study reported fewer adverse neonatal outcomes with lower misoprostol doses, which is consistent with the current study's finding that a lower dose was not associated with exacerbated MSL severity while achieving successful induction.^{12,14} Research also suggests that MSL is often influenced by the duration of PROM and maternal factors as well as the induction agent dosage.¹⁵ In our study, however, there was a statistically significant difference in MSL severity between the 25 µg and 50 µg groups ($p < 0.001$), with the 50 µg group demonstrating a shift toward more severe MSL. This suggests that dosage may be independently associated with MSL severity,

though unadjusted confounders such as PROM duration and gestational age may also play a role.

At the same time, there was a notable difference in the mode of delivery ($p < 0.001$). A significantly greater proportion of spontaneous vaginal deliveries (86%) was recorded with the 25 µg regimen than with the 50 µg dosage (52%), with the rate of lower segment caesarean section (LSCS) being almost triple (48% vs. 14%). American College of Obstetricians and Gynecologists (ACOG) guidelines recommend a low-dose misoprostol regimen (25-50 µg) for labor induction due to its favorable safety profile.¹⁴ In the current study, the lower 25 µg dose was associated with a higher rate of spontaneous vaginal delivery, aligning with this safety principle. This further aligns with other national and international evidence suggesting better maternal safety profiles with lower-dose regimens.^{14,16} The higher LSCS rate with 50 µg might be indicative of increased uterine hyperstimulation and fetal heart rate abnormalities, as reported elsewhere,¹⁷ necessitating operative delivery.

In the Pakistani context, Shafqat et al. (2023) reported that low-dose vaginal misoprostol

(25 µg) was associated with favorable maternal and fetal outcomes in a tertiary care setting, consistent with current study findings.¹⁶ Similarly, Qayyum et al. (2023) from Civil Hospital Karachi identified MSL as a significant risk factor for adverse perinatal outcomes, underscoring the importance of minimizing iatrogenic exacerbation of MSL during induction.¹⁵ These local data reinforce the potential clinical relevance of current study findings for Pakistani obstetric practice.

Notably, the stratified analysis of each dosage group brings out a pattern. Other clinical parameters, like the number of doses needed, final mode of delivery, and gravida status, did not have a statistically significant association with the severity of MSL. In the 25 µg and 50 µg groups, the *p*-values of these sub-analyses (ranging between 0.216 and 0.945) indicated that the MSL grade that a woman attained was not dependent on these sub-factors. This supports the interpretation that the dosage may be the dominant factor associated with the observed difference in MSL severity, and that these influences do not appear to act as modifiers within a given dosage regimen. The result does not support the previous hypothesis that Grade II MSL was associated with the need to administer the second dose in the 25 µg group, as the association was not statistically significant (*p* = 0.216).

The results have specific implications in contexts such as Pakistan, where MSL is a known risk factor for neonatal morbidity. It seems the 25 µg regimen has two benefits: it induces labor, while at the same time being associated with less severe meconium passage and the highest chance of vaginal delivery.

This is in line with the WHO and FIGO recommendations for cautious, low-dose protocols for induction,^{8,10} principles which current study findings support. In the Pakistani context, where studies have identified MSL as a key risk factor for poor neonatal outcomes,^{12,13} using a 25 µg regimen appears prudent. It achieves induction without apparently exacerbating MSL severity, while maximizing the chance of vaginal delivery and minimizing surgical risk.

This study had several limitations. The relatively small sample size (*n*=100) from a single centre limits generalizability. The non-randomized design means that differences between groups may reflect physician selection preferences rather than the dose itself, and important confounders such as exact gestational age and duration of membrane rupture were not adjusted for due to missing data. Additionally, direct neonatal safety outcomes were not assessed. Therefore, the study can demonstrate associations but cannot establish causation, and the

findings should be interpreted as hypothesis-generating.

Future research should involve larger sample sizes across multiple centres to ensure the findings are representative and applicable to broader populations. Randomized controlled trials comparing different dosages of misoprostol with other induction agents could provide more robust evidence for clinical guidelines. Studies focusing on the long-term effects of different misoprostol dosages on maternal and neonatal health would offer valuable insights. Research into the pharmacological mechanisms of misoprostol at varying dosages could help optimize its use in specific clinical scenarios. Expanding studies to include populations from various geographical, ethnic, and socioeconomic backgrounds can enhance the generalizability of results.

Conclusion

The 25 µg dosage regimen was associated with less severe MSL and a higher proportion of spontaneous vaginal delivery in this sample. Given the observational study design, these hypothesis-generating findings suggest that lower-dose regimens may offer a favorable clinical profile; however, randomized controlled trials with adjustment for confounders and direct neonatal safety outcomes are required before recommending routine use.

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Availability of Data: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical Approval: The Institutional Review Board of Kohi Goth Women's Hospital, Karachi approved the study via letter no. IRB/22062024/011 dated 01/05/2024.

Conflict of Interest: None declared.

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