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Study of combination of oxytocin and misoprostol for reducing postpartum blood loss: A randomized comparative study

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Abstract
Introduction: Postpartum hemorrhage (PPH) is a leading cause of maternal morbidity and mortality worldwide. Active management of the third stage of labor (AMTSL) with oxytocin is standard practice, but limitations in storage and administration have prompted evaluation of misoprostol as an adjunct.
Aim: To assess the efficacy of combining intramuscular oxytocin with sublingual misoprostol in reducing postpartum blood loss and minimizing the need for additional uterotonics compared to oxytocin alone.
Methods: A prospective, randomized study was conducted on 100 women delivering vaginally at term. Group 1 (n = 50) received 10 units of intramuscular oxytocin, while Group 2 (n = 50) received oxytocin plus 600 µg sublingual misoprostol. Demographic variables, hemoglobin levels, blood loss, uterine tone, need for additional uterotonics, and postpartum complications were analyzed.
Results: Mean blood loss was significantly lower in Group 2 (338.3±108.2 ml) compared to Group 1 (426.7±124.6 ml, p = 0.001). The requirement for additional uterotonics was also reduced in Group 2 (18%) versus Group 1 (40%, p = 0.0098). No significant differences were observed in transfusion rates, PPH incidence, or postpartum complications such as shivering and pyrexia.
Conclusion: The addition of sublingual misoprostol to intramuscular oxytocin effectively reduces postpartum blood loss and the need for supplementary uterotonics without increasing adverse outcomes. Combination therapy offers a safe and practical strategy for PPH prevention, particularly in resource-limited settings.

Keywords: Postpartum hemorrhage, oxytocin, misoprostol

Introduction

Postpartum hemorrhage (PPH) is a major obstetric emergency and continues to be one of the leading causes of maternal morbidity and mortality worldwide, accounting for nearly one-quarter of maternal deaths annually [1, 2]. The burden is disproportionately higher in low-and middle-income countries, where limited access to timely interventions and blood transfusion services exacerbates outcomes [3]. Active management of the third stage of labor (AMTSL) has been universally recommended to reduce the risk of PPH. Oxytocin, administered intramuscularly or intravenously, is the first-line uterotonic agent due to its rapid onset of action and proven efficacy [4, 5]. However, oxytocin requires cold-chain storage and parenteral administration, which may limit its availability and practicality in resource-constrained settings [6]. Misoprostol, a prostaglandin E1 analogue, offers several advantages: it is inexpensive, stable at room temperature, and can be administered via oral, sublingual, rectal, or vaginal routes [7, 8]. Studies have suggested that misoprostol, when used in combination with oxytocin, may enhance uterine contractility, reduce postpartum blood loss, and lower the need for additional uterotonics compared to oxytocin alone [9, 10]. Nevertheless, concerns remain regarding its side effects, particularly shivering and pyrexia, which warrant careful evaluation of its safety profile [11]. Given these considerations, the present study was undertaken to evaluate the efficacy of combining intramuscular oxytocin with sublingual misoprostol in the active management of the third stage of labor. The study specifically aimed to assess reductions in postpartum blood loss, changes in hemoglobin levels, uterine tone, requirement for additional uterotonics, and incidence of postpartum complications, thereby contributing to evidence-based strategies for optimizing maternal outcomes in obstetric practice.

Aims and Objectives

Aim

To evaluate the efficacy of combining intramuscular oxytocin with sublingual misoprostol in the active management of the third stage of labor, specifically in reducing postpartum blood loss and minimizing the need for additional uterotonics, compared to oxytocin alone.

Objectives

1. To compare demographic and baseline clinical variables (age, parity, gestational age, BMI, and hemoglobin levels) between the two study groups to ensure comparability.
2. To assess the mean blood loss and changes in hemoglobin levels following delivery in women receiving oxytocin alone versus oxytocin with misoprostol.
3. To evaluate uterine tone and the requirement for additional uterotonics in both groups.
4. To determine the incidence of postpartum hemorrhage (PPH) and postpartum complications (shivering, pyrexia) associated with the use of misoprostol in combination with oxytocin.

Materials and Methods

Study Design

This was a prospective, randomized, comparative study conducted in the Department of Obstetrics and Gynecology between the study period of 01/01/2024 to 1/12/2025. Ethical clearance was obtained from the institutional review board prior to commencement. Written informed consent was obtained from all participants.

Study Population

A total of 100 women fulfilling the inclusion criteria were enrolled and randomized into two groups:

- **Group 1 (n = 50):** Received 10 units of intramuscular oxytocin immediately after delivery of the anterior shoulder.
- **Group 2 (n = 50):** Received 10 units of intramuscular oxytocin plus 600 µg of sublingual misoprostol.

Inclusion Criteria

- Singleton pregnancy
- Term gestation (37-40 weeks)
- Vaginal delivery
- Hemodynamically stable women

Exclusion Criteria

- Women with hypertensive disorders of pregnancy
- Known coagulopathies
- History of previous postpartum hemorrhage
- Multiple gestations
- Cesarean deliveries

Randomization

Participants were allocated into two groups using a computer-generated random sequence. Allocation concealment was maintained through sealed opaque envelopes.

Data Collection

Baseline demographic and clinical variables (age, parity, gestational age, BMI, hemoglobin levels) were recorded. Blood loss was measured using calibrated collection drapes and weighing of soaked pads. Hemoglobin levels were assessed pre-delivery and 24 hours post-delivery. Uterine tone, need for additional uterotonics, and postpartum complications (PPH, shivering, pyrexia) were documented.

Operational Definitions

- **Postpartum hemorrhage (PPH):** Defined as blood loss ≥500 ml within 24 hours after vaginal delivery, in accordance with WHO criteria[12].
- **Uterine atony:** Failure of the uterus to contract adequately after delivery, identified clinically by a soft, boggy uterus on palpation[13].
- **Additional uterotonics:** Requirement of any uterotonic agent beyond the standard regimen (oxytocin±misoprostol), such as ergometrine or carboprost[14].
- **Postpartum pyrexia:** Temperature ≥38 °C occurring within 24 hours postpartum, excluding other infectious causes[15].

Statistical Analysis

Data were analyzed using SPSS software version 22.0. Continuous variables were expressed as mean±standard deviation and compared using Student's t-test. Categorical variables were analyzed using Chi-square test or Fisher's exact test as appropriate. A p-value <0.05 was considered statistically significant.

Observation and Result

Table 1: Demographic Variables

Sr. No	Variable	Group 1 (n = 50)	Group 2 (n = 50)	Total (n = 100)	χ^2	p-value
1	Age (years)				6.67	0.0098
	a. 20-25	28 (56%)	14 (28%)	42 (42%)		
	b. 26-30	22 (44%)	36 (72%)	58 (58%)		
2	Parity				0.23	0.8890
	a. 1	18 (36%)	16 (32%)	34 (34%)		
	b. 2	25 (50%)	27 (54%)	52 (52%)		
	c. 3	7 (14%)	7 (14%)	14 (14%)		
3	Gestational age				6.72	0.0810
	a. 37 weeks	5 (10%)	4 (8%)	9 (9%)		
	b. 38 weeks	7 (14%)	16 (32%)	23 (23%)		
	c. 39 weeks	30 (60%)	25 (50%)	55 (55%)		
	d. 40 weeks	8 (16%)	5 (10%)	13 (13%)		
4	BMI (kg/m^2)				1.13	0.5680
	a. 18.5-24.9	20 (40%)	24 (48%)	44 (44%)		
	b. 25-29.9	19 (38%)	15 (30%)	34 (34%)		
	c. 30-34.9	11 (22%)	11 (22%)	22 (22%)		

The age distribution between the two groups showed a statistically significant difference. In Group 1, the majority of women were younger (56% aged 20-25 years), whereas in Group 2, most were slightly older (72% aged 26-30 years). This difference was significant ($\chi^2 = 6.67$, $p = 0.0098$), suggesting that age was not evenly matched across groups. Parity and gestational age, however, did not differ significantly between the groups. Both groups had similar proportions of primiparous and multiparous women ($p = 0.8890$), and gestational age distribution was comparable ($p = 0.0810$). Likewise, BMI categories were balanced between the groups ($p = 0.5680$). These findings indicate that apart from age, baseline demographic characteristics were largely similar.

Table 2: Hemoglobin and Blood Loss

Sr. No	Variable	Group 1 (n = 50)	Group 2 (n = 50)	Total (n = 100)	χ^2	p-value
1	Pre-delivery Hb (gm%) a. 8 to 9 b. 9.1 to 10 c. 10.1 to 11 d. 11.1 to 12 e. 12.1 to 13	 1 (2%) 14 (28%) 23 (46%) 8 (16%) 4 (8%)	 2 (4%) 4 (8%) 31 (62%) 10 (20%) 3 (6%)	 3 (3%) 18 (18%) 54 (54%) 18 (18%) 7 (7%)	11.21	0.0240
2	Post-delivery Hb (gm%) a. 8 to 9 b. 9.1 to 10 c. 10.1 to 11 d. 11.1 to 12 e. 12.1 to 13	 1 (2%) 8 (16%) 27 (54%) 9 (18%) 5 (10%)	 2 (4%) 4 (8%) 31 (62%) 10 (20%) 3 (6%)	 3 (3%) 12 (12%) 58 (58%) 19 (19%) 8 (8%)	6.87	0.1430
3	blood loss (Mean ± SD)	426.7±124.6	338.3±108.2	-	t-statistic = 3.42	0.0010
4	No. of blood units transfused a. 0 b. 1 c. 2	 31 (62%) 15 (30%) 3 (6%)	 37 (74%) 11 (22%) 2 (4%)	 68 (68%) 26 (26%) 5 (5%)	1.54	0.4630

Pre-delivery hemoglobin levels differed significantly between the groups ($p = 0.0240$). Group 2 had a higher proportion of women with hemoglobin levels above 10 g/dl compared to Group 1, which may have influenced tolerance to blood loss. Post-delivery hemoglobin values, however, did not show a statistically significant difference ($p = 0.1430$), indicating that both groups experienced comparable declines after delivery. Blood loss was markedly reduced in Group 2 (mean 338.3±108.2 ml) compared to Group 1 (426.7±124.6 ml), and this difference was highly significant ($t = 3.42$, $p = 0.0010$). Despite this, the need for blood transfusion was not significantly different between groups ($p = 0.4630$), suggesting that while misoprostol reduced average blood loss, it did not substantially alter transfusion requirements.

Table 3: Uterine Tone and Uterotonics

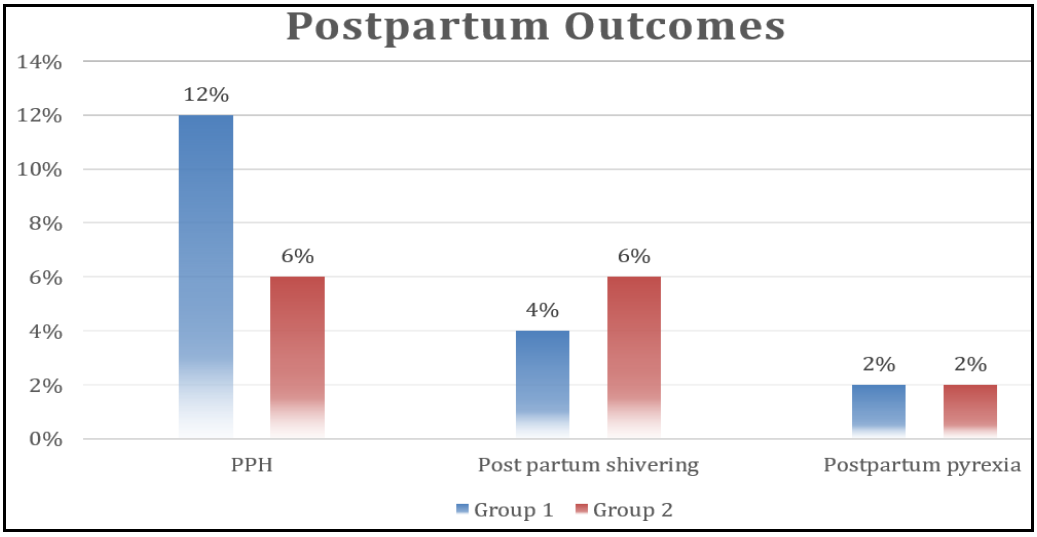
Sr. No	Variable	Group 1 (n = 50)	Group 2 (n = 50)	Total (n = 100)	χ^2	p-value
1	Uterine tone Atonic a. Atonic b. Well contracted	 3 (6%) 47 (94%)	 2 (4%) 48 (96%)	 5 (5%) 70 (70%)	0.21	0.6460
2	Need for additional uterotonics a. No b. Yes	 30 (60%) 20 (40%)	 41 (82%) 9 (18%)	 71 (71%) 29 (29%)	6.67	0.0098

Uterine tone was well contracted in the majority of women in both groups, with no significant difference ($p = 0.6460$). However, the need for additional uterotonics was significantly lower in Group 2 (18%) compared to Group 1 (40%) ($\chi^2 = 6.67$, $p = 0.0098$). This highlights that the addition of misoprostol reduced the requirement for supplementary uterotonic agents, reinforcing its role in improving uterine contractility and minimizing atonic tendencies.

Table 4: Postpartum Outcomes

Sr. No	Variable	Group 1 (n = 50)	Group 2 (n = 50)	Total (n = 100)	χ^2	p-value
1	PPH a. No b. Yes	 44 (88%) 6 (12%)	 47 (94%) 3 (6%)	 91 (91%) 9 (9%)	1.07	0.3010
2	Post partum shivering a. No b. Yes	 48 (96%) 2 (4%)	 47 (94%) 3 (6%)	 95 (95%) 5 (5%)	0.21	0.6460
3	Postpartum pyrexia a. No b. Yes	 49 (98%) 1 (2%)	 49 (98%) 1 (2%)	 98 (98%) 2 (2%)	0.00	1.0000

Postpartum hemorrhage (PPH) occurred less frequently in Group 2 (6%) compared to Group 1 (12%), though this difference was not statistically significant ($p = 0.3010$). Similarly, postpartum shivering and pyrexia were rare and comparable between groups, with no significant differences ($p = 0.6460$ and $p = 1.0000$, respectively). These findings suggest that misoprostol did not increase adverse postpartum outcomes, and its safety profile was similar to oxytocin alone.



Graph 1: Postpartum Outcomes

Discussion

The present study evaluated the efficacy of combining intramuscular oxytocin with sublingual misoprostol in the active management of the third stage of labor. Our findings demonstrated that mean blood loss was significantly reduced in the combination group (338.3±108.2 ml) compared to oxytocin alone (426.7±124.6 ml, p = 0.001). Additionally, the requirement for additional uterotonics was lower in the oxytocin-misoprostol group (18%) versus oxytocin alone (40%, p = 0.0098). These results suggest that misoprostol enhances uterotonic efficacy when used alongside oxytocin. Similar reductions in blood loss have been reported in randomized trials. A study by Lokugamage *et al*. found that sublingual misoprostol combined with oxytocin significantly decreased postpartum blood loss compared to oxytocin alone [16]. Another multicenter trial conducted in Egypt demonstrated that misoprostol adjunct therapy reduced the incidence of PPH and lowered the need for additional uterotonics [17]. In contrast, some studies have shown no significant difference in transfusion requirements despite reduced blood loss, consistent with our observation that transfusion rates were comparable between groups [18]. Regarding uterine tone, our study found no significant difference between groups, but the reduced need for supplementary uterotonics in the misoprostol group aligns with findings by Villar *et al*., who reported improved uterine contractility with combined therapy [19]. Postpartum complications such as shivering and pyrexia were rare and not significantly different between groups, corroborating the safety profile described in other trials [20].

The observed reduction in blood loss with misoprostol adjunct therapy may be explained by its pharmacological action. Misoprostol, a prostaglandin E1 analogue, binds to myometrial receptors and induces strong, sustained uterine contractions [21]. When combined with oxytocin, which acts via G-protein coupled receptors to increase intracellular calcium and stimulate rhythmic contractions [22], the dual mechanism provides both rapid onset (oxytocin) and prolonged contractility (misoprostol). This synergistic effect likely accounts for the reduced incidence of uterine atony and diminished blood loss. Furthermore, misoprostol's sublingual route ensures rapid absorption and high bioavailability, leading to effective uterine stimulation even in settings where parenteral administration may be delayed [23]. The absence of increased adverse events in our study supports the notion that misoprostol, when used judiciously, is a safe adjunct to oxytocin in AMTSL. Our findings reinforce the role of misoprostol as a valuable adjunct in resource-limited settings where oxytocin availability or cold-chain storage may be challenging. The combination therapy not only reduces blood loss but also minimizes the need for additional uterotonics, thereby simplifying postpartum management.

Conclusion

The addition of sublingual misoprostol to intramuscular oxytocin significantly reduced postpartum blood loss and lowered the need for additional uterotonics, without increasing adverse maternal outcomes. Although transfusion rates and PPH incidence were not statistically different, the overall reduction in blood loss highlights the benefit of combination therapy. Given its stability, ease of use, and favorable safety profile, misoprostol is a valuable adjunct to oxytocin, especially in resource-limited settings. Larger multicenter studies are recommended to confirm these findings and guide routine practice.

Conflict of Interest

Not available

Financial Support

Not available

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