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Research Article

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Prevention of Immediate Postpartum Hemorrhage by The Combination of Oxytocin And Misoprostol at The Gynaecology-Obstetrics Department of The Ignace Deen National Hospital of Conakry University Hospital

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Abstract

Objective: *This randomised comparative clinical trial aimed to assess the effectiveness and tolerability of combining oxytocin and misoprostol for preventing immediate postpartum haemorrhage (PPH).*

Methodology: *The study was conducted at the Gynaecology-Obstetrics department of Ignace Deen National Hospital. Participants were randomly assigned to two groups: one receiving oxytocin and placebo and the other receiving oxytocin and misoprostol. Blood loss, incidence of PPH, need for blood transfusion, and adverse effects were measured as primary outcomes.*

Results: *Analysis of the data revealed that patients receiving oxytocin and misoprostol had significantly lower blood loss (436 ml vs 533 ml, p=0.02) and a notably reduced incidence of PPH compared to those receiving oxytocin and placebo (11.9% vs 38.5%, p=0.00). The need for blood transfusion was also significantly lower in the misoprostol group (9.2% vs. 20.2%, p=0.02). However, the frequency of maternal death was comparable between the two groups (2.7% vs 3.7%, p=0.70). Adverse effects were mainly observed in the misoprostol group, including chills (58.3%), fever (22.9%), and vomiting (12.5%).*

Conclusion: *Administering 600µg of misoprostol sublingually in addition to the standard 10 IU oxytocin during delivery significantly reduces the incidence of PPH due to uterine atony. This combination therapy demonstrates promising efficacy in preventing postpartum haemorrhage, though close monitoring for potential adverse effects is essential.*

Keywords: Misoprostol, Oxytocin, Postpartum Haemorrhage, Ignace Deen National Hospital.

1. Introduction

Postpartum haemorrhage (PPH) characterised by blood loss exceeding 500 ml, regardless of the mode of delivery and whether externalised or not, remains a critical concern in maternal health [1,2]. The incidence of PPH varies significantly across countries, with reported rates of 10% in France, 5.1% in Canada, 1.4% in Morocco, 4.7% in Togo, and 2.91% in Guinea [3-7]. As the foremost preventable cause of maternal mortality, PPH is primarily associated with uterine atony [1,2,7,8]. Prophylactic administration of oxytocin has proven to be effective in reducing the incidence of PPH [2]. Moreover, some studies have demonstrated the efficacy of administering misoprostol alone in preventing uterine atony during childbirth [9-13]. Additionally, growing evidence supports the synergy between oxytocin and misoprostol, with combined use resulting in a more significant reduction in PPH risk compared to individual administration of these agents [12, 14-17]. However,

certain studies have not validated this finding and suggested further investigation before drawing definitive conclusions [18-19]. Furthermore, limitations in some studies, such as the absence of randomisation, non-compliance with double blinding in some cases, lack of a placebo, inadequate measurement of blood loss, and oversight of adverse effects, have raised the necessity for more rigorous research in this area. Considering these considerations, our study aims to evaluate the efficacy and tolerance of combining oxytocin and misoprostol to prevent immediate postpartum haemorrhage, focusing on parturients at high risk of PPH due to uterine atony.

1.1. Research Question: Does the combination of oxytocin and misoprostol for the prevention of immediate postpartum haemorrhage due to uterine atony reduce the frequency of immediate postpartum haemorrhage (IPPH) in high-risk women compared to oxytocin alone?

1.2. Endpoints: The primary endpoint of this study was the incidence of PPH, defined as the amount of blood lost ≥ 500 ml, within two hours of monitoring in the delivery room. Secondary endpoints included the assessment of blood pressure, pulse rate, haemoglobin levels, occurrences of blood transfusion, evaluation of adverse effects, and the measurement of HPH-related lethality.

2. Methodology

2.1. Study Setting and Population

This double-masked, randomised, comparative superiority clinical trial was conducted at the Ignace Deen National Hospital, University Hospital of Conakry, in the maternity ward from March 1 to July 31, 2022. The hospital's maternity ward operates at level 3 and performs over 6,000 deliveries annually, serving as a vital referral centre for maternal health in Guinea.

The target population for this study consisted of parturients who arrived to give birth at the department during the specified study period. Specifically, the study population included parturients at high risk of uterine atony, carrying full-term pregnancies, and giving birth vaginally in the department during the study period.

2.2. Inclusion Criteria: Participants included in the trial were:

i. Multiparous parturients (parity ≥ 4).
ii. Parturients with prolonged labour (≥ 24 hours) or a history of previous postpartum haemorrhage (PPH).
iii. Parturients with uterine overdistension (multiple pregnancies, large fetus, polyhydramnios) or a myxomatous uterus.
iv. Parturients who delivered vaginally at term in the department during the study period.
v. Parturients who willingly agreed to participate in the study.

2.3. Exclusion Criteria: Participants excluded from the trial were:

i. Parturients presenting with antepartum bleeding or experiencing tearing of soft tissues after childbirth.
ii. Parturients who had delivered by caesarean section or had a contraindication to misoprostol.
iii. Parturients who did not consent to participate in the study.

The informed consent of all patients was obtained, and any contraindications were carefully assessed during labour. Inclusion into the study occurred immediately after the baby's expulsion, ensuring the absence of tearing of the soft tissues.

For comparison, two distinct groups were formed. The first group received a combined treatment of 10 IU of oxytocin and 600µg of misoprostol, administered as three sublingual tablets. Conversely, the second group received 10 IU of oxytocin and three placebo tablets, designed to have an identical appearance to the misoprostol tablets, and were also administered sublingually.

To determine the appropriate sample size for each group, a calculation was performed utilising the following formula:

$$n = \frac{\left(U\alpha\sqrt{2\pi(1-\pi)+U_{2\beta}\sqrt{\pi_N(1-\pi_N)+\pi_R(1-\pi_R)}}\right)^2}{2a}$$

$$\text{with} \quad \Delta=\pi_N-\pi_R$$

Uα=1,96, π=0,5, U2α=1,282, πN=0,4 and πR=0,6 α à 5% et β à 10%.

According to a study conducted in the ward in 2019, the frequency of postpartum haemorrhage due to uterine atony when using oxytocin alone during the third stage of labour was 59%. Thus, investigating the combination of oxytocin and misoprostol becomes highly pertinent, as it can potentially reduce the proportion of postpartum haemorrhage attributed to uterine atony by 20%. After thorough calculations, the study determined that 109 subjects were required to be included in each group to achieve sufficient statistical power. The allocation research team carried out the allocation of treatment random drawing process, ensuring the midwives responsible for monitoring the births and collecting data were unaware of the administered treatment, and the participants were kept blinded to their assigned groups.

Randomisation was performed using a table of random numbers, with each number between 0 and 9 having an equal probability of appearing in the table. The direction of reading the table was fixed, and a pencil was randomly pointed at the table, generating the assignment of participants to different groups. All numbers from 0 to 4 were assigned to receive oxytocin plus misoprostol, while those from 5 to 9 were allocated to the oxytocin plus placebo group.

Oxytocin was administered via intramuscular injection into the anterolateral aspect of one of the woman's thighs immediately after the baby's delivery. After confirming the absence of another

baby in the womb and ruling out any soft tissue tearing, the midwife who conducted the delivery administered three tablets of either misoprostol or placebo, depending on the assigned group, sublingually.

Monitoring for both groups took place in the department during the first two hours following delivery. The amount of blood lost was collected in a plastic bag under the woman's buttocks and retained for two hours. The blood collected was then measured using a graduated container and compared between the two groups. Additionally, various parameters, such as the frequency of postpartum haemorrhage, adverse effects, blood pressure, pulse rate, blood transfusions, and maternal deaths, were evaluated for both groups (Table 1). The data was collected through clinical examination of the participants, as outlined in Table 1.

Follow-up of postpartum deliveries	Oxytocin + Misoprostol	oxytocin+ placebo
15th minute	Uterine retraction, Amount of blood lost, BP, Pulse, Adverse reactions	Uterine retraction, Amount of blood lost, BP, Pulse, Adverse reactions
30th minute	Uterine retraction, Amount of blood lost, BP, Pulse, Adverse reactions	Uterine retraction, Amount of blood lost, BP, Pulse, Adverse reactions
45th minute	Uterine retraction, Amount of blood lost, BP, Pulse, Adverse reactions	Uterine retraction, Amount of blood lost, BP, Pulse, Adverse reactions
60th minute	Uterine retraction, Amount of blood lost, BP, Pulse, Undesirable effects, Adverse reactions	Uterine retraction, Amount of blood lost, BP, Pulse.
90th minute	Uterine retraction, Amount of blood lost, BP, Pulse, Adverse reactions	Uterine retraction, Amount of blood lost, BP, Pulse, Adverse reactions
120th minute	Uterine retraction, Amount of blood lost, BP, Pulse, Adverse reactions, Haemoglobin levels, Blood transfusion, Death	Uterine retraction, Amount of blood lost, BP, Pulse, Adverse reactions, Haemoglobin levels, Blood transfusion, Death

Table 1: Follow-up of deliveries during the first two hours after delivery

Data collection was stopped after leaving the delivery room. Hospitalised women continued to be monitored, while those who went directly home were asked to return for clinical examination on day six or at any time if needed.

All patients who developed PPH in both groups (placebo and misoprostol) were managed by the protocol in force in the department.

2.4. Statistical analyses

Pearson's Chi2 and the Student's test were used to compare the groups after verification of their application conditions. The 5% significance level was retained. Data analysis was performed using Epi Info version 7 software.

2.5. Limitations of the study

For a better statistical inference, it would have been better to use several centres to consider the variabilities in these centres. Nevertheless, this study has the advantage of providing essential elements for future studies.

5- Ethics: The authorisation of the Ministry of Public Health ethics committee and the participants' informed consent were obtained. For the consent search, we proceeded in two ways depending on whether they were an intellectual woman or not:

• For intellectual women, they were given the consent form so that they could read it themselves and sign it freely if they agreed.

• For illiterate women, the translation of the document was read to them, and those who agreed signed it. Anonymity and confidentiality were respected.

Funding: Funding for the study was provided by the research team

3. Results

In each of the two groups, 109 mothers were included (Figure 1).

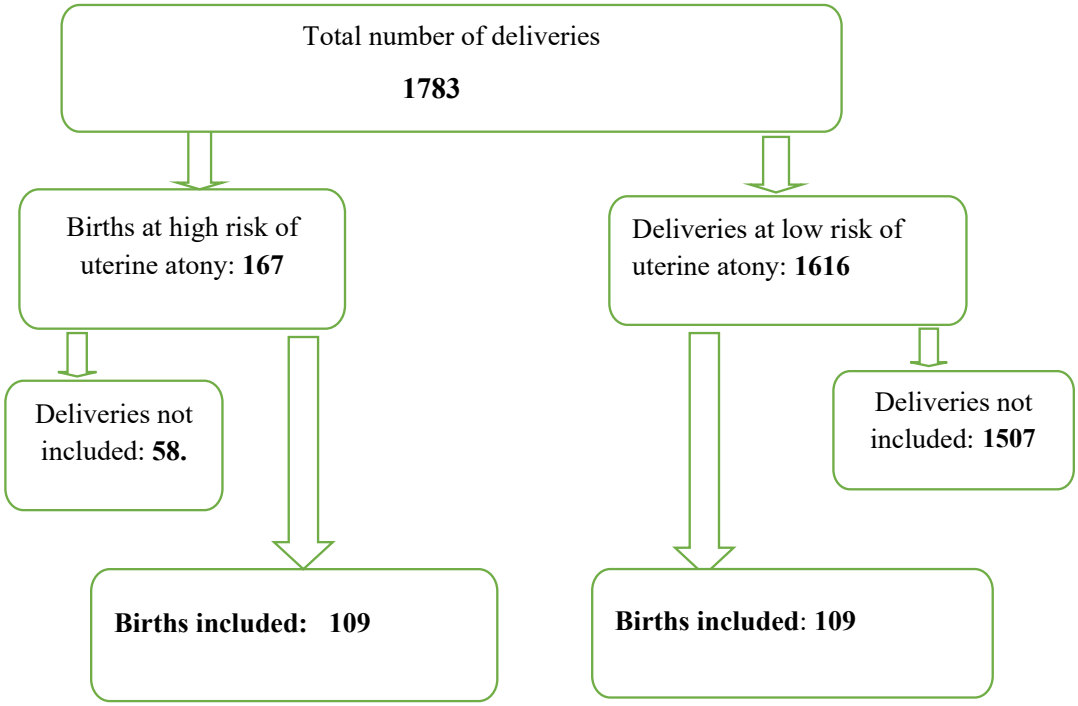

Figure 1: Flowchart

3.1. Characteristics of the patients in the two groups before delivery:

The patients in the two groups (misoprostol and placebo) were comparable before delivery in terms of age (p=0.98), gravidity (p=0.60) and parity (0.62), systolic BP (p= 0.11), diastolic BP (p=0.82) and haemoglobin level (p=0.31) (Table 2).

Characteristics of patients before delivery	Misoprostol	Placebo	p-value
	Mean ± standard deviation		
Age (years)	29.3±6	29.3±7	0,98
Gravidity	3.3±2	3.4±2	0,60
Parity	3.2±2	3.3±2	0,62
Systolic BP per partum (mmHg)	118±2	123±2	0,11
Diastolic BP per partum (mmHg)	75±1	75±1	0,82
THb per partum (g/l)	11±1	11±1	0,31

Table 2: Distribution of patients who received misoprostol versus placebo according to their characteristics before delivery.

3.2. Condition of patients in the immediate postpartum:

Patients who received oxytocin and placebo had more significant blood loss than those who received oxytocin and misoprostol (533 ml vs 436 ml) with p=0.02. Postpartum systolic BP in the misoprostol group (115 mmHg) was significantly lower (p=0.01) than in the placebo group (108 mmHg). The same finding emerges for postpartum diastolic BP with p=0.02. The postpartum Hb level was higher in the misoprostol group (10g vs 9g) than in the placebo group (p=0.03). The women who received misoprostol had a less accelerated heart rate than those who received the placebo (93 beats/min vs 100 beats/min) with p=0.00. (Table 3).

Sequences of layers	Misoprostol	Placebo	p-value
	Mean ± standard deviation		
Amount of blood lost (ml)	436±309	533±275	0,02
Postpartum systolic BP (mmHg)	115±17	108±21	0,01
Postpartum diastolic BP (mmHg)	73±13	69±15	0,02
Postpartum THb (g/l)	10±6	09±2	0,03
Pulse (pulse/min)	93±14	100±12	0,00

Table 3: Distribution of patients who received misoprostol versus placebo according to their postpartum parameters.

4. Maternal prognosis

PPH was significantly more common in women who took oxytocin and placebo than those who received oxytocin and misoprostol (38.5% vs 11.9%) with p=0.00. Blood transfusion was also more frequent in the placebo group than in the misoprostol group (20.2% vs 9.2% p=0.02). On the other hand, the frequency of maternal death was identical between the two groups (2.7% vs 3.7%, p=0.70) (Table 4).

Maternal prognosis	Misoprostol (n=109)	Placebo (n=109)	p-value
	n (%)	n (%)	
PPH			0,00
Yes	13 (11,9)	42 (38,5)	
No	96 (88,1)	67 (61,5)	
Blood transfusion			0.02
Yes	10 (9,2)	22 (20,2)	
No	99 (90,8)	87 (79,8)	
Maternal death			0,70
Yes	3 (2,7)	4 (3,7)	
No	106 (97,3)	105 (96,3)	

Table 4: Distribution of misoprostol versus placebo patients by maternal prognosis

Causes of Death: Among the total of 7 recorded deaths in both groups, all were attributed to haemorrhagic shock.

Diagnoses Included in the Study: The diagnoses selected for patient inclusion revealed that twin pregnancy (33.0%), large foetus (25.7%), and multiparity (24.8%) were the most prevalent conditions observed (Table 5).

Diagnosis	Misoprostol		Placebo	
Treatment	Staff	Percentage	Staff	Percentage
Multiparity	27	24,8	33	30,3
Twin pregnancy	36	33,0	38	34,9
Large fetus	28	25,7	25	22,9
History of PPH	2	1,8	0	0,0
Hydramnios	1	0,9	1	0,9
Extended work	6	5,5	8	7,3
Myomatous uterus	9	8,3	4	3,7
Total	109	100,0	109	100,0

Table 5: Distribution of patients who received misoprostol versus placebo by diagnosis.

Adverse Effects in the Groups: Adverse effects, notably chills (58.3%), fever (22.9%), and vomiting (12.5%), were more frequently observed in the misoprostol group. However, the observed difference in the occurrence of adverse effects between the two groups was not statistically significant (Table 6).

Side effects	Misoprostol		Placebo	
	Staff	Percentage	Staff	Percentage
Shiver	36	80,0	9	20,0
Fever	19	70,4	8	29,6
Abdominal pain	14	53,9	12	46,1
Vomiting	11	64,7	6	35,3
Khi2=5.54, ddl=3, p=0.136				

Table 6: Distribution of patients who received misoprostol versus placebo by occurrence of adverse reactions.

5. Discussion

The scheme used during this study made it possible to evaluate the efficacy and tolerance of the combination of oxytocin and misoprostol in preventing PPH. From a methodological point of view, the randomised nature of the study made it possible to form two groups comparable in terms of age (p=0.98), gravidity (p=0.60), parity (p=0.62), systolic (p=0.11), and diastolic (p=0.82), and Hb levels (p=0.31). Double-blinding and standardisation of follow-up procedures also allowed it to follow both groups and collect data similarly for all study participants. The differences thus observed between the two groups can therefore be validly attributed to the treatment and extrapolated to the target population.

The frequency of PPH in patients who received oxytocin and misoprostol was significantly lower than that observed in patients who received oxytocin and placebo (11.9% vs 38.5%, p=0 .00), with a difference of 26.6%. This difference is more significant than the 20% threshold initially desired to have a genuine interest. The frequency of PPH recorded in patients who received oxytocin and misoprostol is also lower than that (59%) reported in the same department in 2019 when oxytocin alone is used for the active management of the third period of childbirth [7].

The effectiveness of the combination of oxytocin and misoprostol in preventing PPH has also been reported by several authors, regardless of the delivery route. Morfaw et al., in their study on the prevention of PPH, reported that the combination of oxytocin and misoprostol significantly reduced the risk of PPH without affecting the frequency of blood transfusion and maternal deaths [14]. According to Fekih et al., in a randomised clinical trial on the interest of misoprostol in the prevention of immediate PPH in the event of caesarean section, it appears that misoprostol at a dose of 200 µg by sublingual route associated with oxytocin is effective in preventing postpartum haemorrhage in caesarean delivery with minor side effects [12]. In contrast, misoprostol administered alone was less effective in preventing uterine atony than oxytocin alone [13].

This reduction in the frequency of PPH is explained by a synergy of action between oxytocin and misoprostol at the origin of early, long-lasting, and intense uterine contractions. Indeed, according to Fekih et al, some studies have highlighted the synergy between these two classes of hormones, and it has been shown that prostaglandins stimulate the production of oxytocin receptors [12].

The average amount of blood lost by the patients who received oxytocin and the placebo is greater than the threshold of 500 ml used to speak of PPH. These more significant blood losses (533 ml vs 436 ml, p=0.02) were responsible for the lower blood pressure and Hb levels and a higher frequency of blood transfusion in patients who received l oxytocin and placebo. This same observation was made by Fekih et al., who reported blood loss (852.52cc±295.08 vs 669.68cc±333.01; p<0.01) and a fall in haemoglobin more significant in patients who received oxytocin alone [12]. Pakniat et al., in a study comparing three groups (20 IU of oxytocin for the first group, 400µg of misoprostol for the 2nd and 200µg of misoprostol + 5IU of oxytocin for the 3rd), also reported that the use of lower dose of misoprostol-oxytocin combined significantly reduced the amount of blood loss during and after caesarean section compared to the higher dose of oxytocin and misoprostol alone [15].

On the other hand, they did not note a significant difference in mean arterial pressure (p = 0.38) and heart rate (p = 0.23) between the different groups. Fawole et al., in a randomised clinical trial (400µg misoprostol plus oxytocin versus placebo plus oxytocin), reported a slight reduction in blood loss during the third stage of labour in the misoprostol group, but the effects were not statistically significant [18]. The study by Hofmeyr et al. did not confirm a beneficial effect of the administration of 400 µg of misoprostol, in addition to routine uterotonic treatment during the third stage of labour [19]. According to Zuberi et al., adding 600 µg of misoprostol sublingually to standard PPH treatments reduces postpartum blood loss, a less significant drop in postpartum haemoglobin level, and a lower need for additional interventions [16]. Walraven et al., in their study which aimed to compare the addition of 600 µg of misoprostol (200 µg orally and 400 µg sublingually) to routine treatment of PPH with a placebo, reported blood loss lower averages in patients who received 600 µg of misoprostol (325 ml vs 410 ml) [17].

Adverse effects dominated by Chills, fever and vomiting were more

frequently observed in patients who received misoprostol, but the difference was insignificant. The same observation was made by Fekih and Pakniat, who speaks of minor side effects in the event of an oxytocin-misoprostol association [12,15]. In the same order, Zuberi, Hofmeyr and Walraven reported a significantly higher rate of transient chills and fever in women receiving misoprostol but without any severity [16-18]. During their study, Tessier et al. reported that misoprostol is less effective than oxytocics in PPH prophylaxis and is associated with frequent and poorly tolerated maternal side effects (severe tremors, fever, and diarrhoea) [20]. According to Leduc et al., there is a typical dose-response relationship between the dose of misoprostol administered and the risk of side effects with pyrexia more common when the dose of misoprostol exceeds 600 µg. Garrigue et al. also noted misoprostol's significantly more frequent side effects, including diarrhoea, nausea and vomiting, and tremors [21,13].

The frequency of maternal death was identical between the two groups thanks to the rigorous follow-up that all women benefited from during the study with the quantification of blood loss, which made it possible to diagnose PPH cases early and provide adequate care. All the deaths occurred in a picture of haemorrhagic shock following a lack of blood products, thus confirming the data in the literature according to which PPH constitutes the first cause of maternal death, According to Say and al, the proportion of deaths attributable to obstetric haemorrhage is 16% for all developed countries, two-thirds of which are related to PPH [1,2,7,8,22].

The study's findings revealed that patients who received oxytocin and the placebo experienced average blood loss exceeding the 500 ml threshold used to diagnose PPH. These substantial blood losses (533 ml vs 436 ml, p=0.02) were associated with lower blood pressure and haemoglobin levels, leading to a higher frequency of blood transfusions in this group. Similar observations were reported by Fekih et al., who observed more significant blood loss (852.52 cc±295.08 vs 669.68 cc±333.01; p<0.01) and a more significant decline in haemoglobin levels in patients receiving oxytocin alone [12]. Pakniat et al., in their study comparing three groups (20 IU of oxytocin for the first group, 400 µg of misoprostol for the 2nd, and 200 µg of misoprostol + 5 IU of oxytocin for the 3rd), also found that using a lower dose of combined misoprostol-oxytocin significantly reduced blood loss during and after caesarean sections compared to higher doses of oxytocin and misoprostol alone [15]. However, they did not observe a significant difference in mean arterial pressure (p = 0.38) and heart rate (p = 0.23) between the different groups. Fawole et al., in a randomised clinical trial (400 µg misoprostol plus oxytocin versus placebo plus oxytocin), reported a slight reduction in blood loss during the third stage of labour in the misoprostol group, but the effects were not statistically significant. Hofmeyr et al.'s study did not confirm the beneficial effect of administering 400 µg of misoprostol in addition to routine uterotonic treatment during the third stage of labour [18,19]. However, according to Zuberi et al., adding 600 µg of misoprostol sublingually to standard PPH treatments reduces postpartum blood loss, leads to a less significant drop in postpartum haemoglobin levels, and lowers the need for additional interventions [16]. Similarly, Walraven et al., in their study comparing the addition of 600 µg of misoprostol (200 µg orally and 400 µg sublingually) to routine PPH treatment with a placebo, reported lower average blood loss in patients who received 600 µg of misoprostol (325 ml vs. 410 ml) [17].

Regarding adverse effects, chills, fever, and vomiting were more frequently observed in patients who received misoprostol, but the difference was insignificant. Similar observations were made by Fekih and Pakniat, who mentioned minor side effects associated with the oxytocin-misoprostol combination [12,15]. Zuberi, Hofmeyr, and Walraven also reported a significantly higher rate of transient chills and fever in women receiving misoprostol without any severe adverse effects [16-18]. During their study, Tessier et al. reported that misoprostol is less effective than other oxytocics in PPH prophylaxis and is associated with frequent and poorly tolerated maternal side effects such as severe tremors, fever, and diarrhoea. Leduc et al. suggested a typical dose-response relationship between the dose of misoprostol administered and the risk of side effects, with pyrexia more common when the amount exceeds 600 µg [20,21]. Garrigue et al. also observed significantly more frequent side effects with misoprostol, including diarrhoea, nausea and vomiting, and tremors [13].

The frequency of maternal death was identical in both groups, thanks to rigorous follow-up and quantification of blood loss that enabled early diagnosis and adequate care for PPH cases. All deaths occurred due to haemorrhagic shock resulting from a lack of blood products, confirming the data in the literature stating that PPH constitutes the leading cause of maternal death [1,2,7,8]. According to Say et al., the proportion of deaths attributable to obstetric haemorrhage is 16% for all developed countries, with two-thirds related to PPH [22].

6. Conclusion

In conclusion, the adjunctive administration of 600µg of misoprostol sublingually, in conjunction with the standard 10 IU of oxytocin used in active management of the third stage of labour, demonstrates a significant reduction in blood loss during the postpartum period. Moreover, this combination therapy proves effective in lowering the incidence of postpartum haemorrhage caused by uterine atony, thereby reducing the need for blood transfusions. The findings from this study highlight the potential benefits of this combined approach in improving maternal outcomes and supporting its implementation as a preventive measure for immediate postpartum haemorrhage.

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