

COMPARISON OF INTRAUTERINE MISOPROSTOL WITH INTRAVENOUS OXYTOCIN VERSUS INTRAVENOUS OXYTOCIN ALONE TO PREVENT PRIMARY POSTPARTUM HEMORRHAGE DURING CESAREAN SECTION

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Abstract

Background: Postpartum hemorrhage (PPH) ranks among the causes of maternal morbidity and mortality, and is a significant issue with cesarean delivery. Uterine atony is the other major cause of excessive blood loss, and other uterotonic drugs could help increase uterine tone and decrease perioperative blood loss.

Objective: To compare the mean blood loss with intrauterine misoprostol with intravenous oxytocin and intravenous oxytocin alone during cesarean section.

Methods: This was a randomized controlled trial that was carried out at Department of Obstetrics and Gynecology, POF hospital, Wah Cantt from April 2025 to July 2025. A total of 60 women in lower segment cesarean section were randomly divided into two groups of equal numbers. Group A got 10 IU intravenous oxytocin, and Group B got 10 IU intravenous oxytocin plus 400 µg intrauterine misoprostol upon delivery of the placentas. Intraoperative and 24-hour postoperative blood loss was measured by gravimetric and volumetric methods. SPSS version 25 was used for analysis of data.

Results: Mean intraoperative blood loss was lower in Group B than Group A (310.2 ± 38.6 vs. 380.5 ± 45.2 mL). Similarly, 24-hour postoperative blood loss was lower in Group B (112.4 ± 18.3 vs. 145.2 ± 22.1 mL). Total measured blood loss was 422.6 ± 43.1 mL in Group B compared with 525.7 ± 52.4 mL in Group A ($p < 0.001$).

Conclusion: In this study, the postoperative bleeding volume was significantly decreased in the group receiving intrauterine misoprostol in addition to intravenous oxytocin during cesarean section.

INTRODUCTION

Postpartum hemorrhage (PPH) is a serious obstetric condition and a significant contributor to maternal morbidity and mortality in the world. This is defined as heavy bleeding after giving birth. Today, the definition of PPH is a total blood loss of 1000 mL or more and/or clinical signs and

symptoms of hypovolemia, regardless of the mode of delivery. Primary PPH happens within the first 24 hours after childbirth and secondary PPH can happen between 24 hours and up to 12 weeks after birth [1]. The incidence of PPH is around 2–4% during a vaginal delivery and 6% during a cesarean section. The most frequent cause is uterine atony,

which causes over half of the cases, followed by retained placental tissue, genital tract trauma, coagulation disorders and uterine rupture [2].

The main significance of uterine atony is during cesarean delivery when there is a possibility of large blood loss if the uterus doesn't contract properly. Hence, oxytocin is a common prophylactic uterotonic agent routinely used to encourage uterine contractility and prevent PPH. No evidence exists to suggest that the use of intravenous oxytocin for the prevention of PPH during vaginal birth is more harmful or has an increased adverse-effect profile compared to intramuscular oxytocin, and the evidence suggests it is more effective at preventing PPH [3,4]. But, even though it has a proven track, the efficacy of oxytocin alone may not be enough for some women, especially those who have an elevated risk of uterine atony and heavy bleeding.

Another uterotonic agent that has been studied for the prevention of PPH is misoprostol, a prostaglandin E1 analogue, especially in resource-poor areas. Studies of women who are having elective C-sections have shown that the use of misoprostol can be beneficial for reducing the amount of blood loss after delivery, and, in certain situations, being more effective at protecting women from excessive bleeding as a prophylactic treatment than intravenous oxytocin alone [5]. Misoprostol has also been combined with oxytocin to improve contractions of the uterus, and to further decrease blood loss. Data from low-resource areas show that the two drug combination may lead to better obstetric outcomes, with fewer and less severe cases of excessive blood loss than with oxytocin alone [6]. There are a number of clinical reports showing beneficial effects of misoprostol augmentation with oxytocin. El-Hammroni et al. reported a mean of 511.9 ± 23.7 mL and 457.4 ± 21.5 mL blood loss for oxytocin and misoprostol plus oxytocin, respectively, which was statistically different [7]. Alalfy et al. also investigated the use of intrauterine misoprostol in cesarean section and concluded that it is effective to decrease the incidence of primary PPH [8]. The results of the current study are also consistent with a systematic review and meta-analysis by Maged et al., which

aimed to determine the effect of misoprostol on blood loss during elective cesarean section done on women and included evidence showing that misoprostol has a blood loss reducing effect [9].

Use of misoprostol alone or in combination with oxytocin is also relevant and important since the efficacy of misoprostol needs to be balanced with the dose-related adverse effects. In the context of cesarean section, Srirangamwong et al. studied the effect of various doses of misoprostol mixed with oxytocin on PPH prevention, thus giving further evidence of the importance of dose optimisation in PPH prophylaxis [10]. While there is existing evidence to support the use of misoprostol, differences in patient populations, methods of administration, dosage, and clinical use, combined with the use of oxytocin, necessitate further evaluation.

Hence, the aim of this study was to compare the effectiveness of oxytocin alone and misoprostol in addition to oxytocin for the prevention of PH. This study will assess the total blood loss and other clinical outcomes in the study population to determine if using misoprostol with routine oxytocin prophylaxis will also decrease postpartum blood loss and enhance obstetric outcomes.

1.Objective

To compare the mean blood loss with intrauterine misoprostol with intravenous oxytocin and intravenous oxytocin alone during cesarean section.

2.Methodology

This was a randomized controlled trial that was carried out at Department of Obstetrics and Gynecology, POF hospital, Wah Cantt from April 2025 to July 2025. In total 60 lower segment cesarean section (LSCS) women were included. Based on previous reported mean blood loss values, the sample size was determined at 80% power and 5% level of significance, but 60 participants were enrolled to have enough blood loss data for comparison. The participants were sampled using non-probability consecutive sampling and randomly divided by lottery into two groups of 30 participants. Group A was given 10 IU intravenous oxytocin diluted in 250 mL

normal saline for 30 minutes after the delivery of the neonate. Placental delivery was followed by a 400 µg intrauterine dose of misoprostol to Group B, along with the same oxytocin dosage.

3.1 Inclusion Criteria

All women, aged 18–40 years, who had parity <5 and gestational age >32 weeks who had undergone emergency or elective lower segment cesarean section (LSCS) were included.

3.2 Exclusion Criteria

Women who had vaginal delivery, pre-existing bleeding or clotting disorders, therapeutic anti-coagulants, BMI <18.5 kg/m², another trial, or renal failure, cardiac abnormalities or active liver disease were excluded.

3.3 Data Collection Procedure

The Institutional Ethical Review Board approved women having lower segment cesarean section who were eligible for the study were recruited after taking written informed consent from them from the obstetrics and gynecology department. Structured proforma was used to record the demographic and obstetric data such as age, height, weight, BMI, gestational age, parity, indication for cesarean section. The participants were randomly divided by the lottery method into 3 groups, Group A and Group B each consisting of 30 women. After neonatal delivery, group A was given 10 IU oxytocin in 250 mL of 0.9% normal saline via intravenous infusion for 30 minutes. Placental removal and exteriorization/cleansing of the uterus were followed by intrauterine administration of 400 µg oxytocin to group B as well as the same oxytocin schedule. Blood loss was determined intraoperatively and in the first 24 postoperative hours with pre-weighed pads, gauzes and drapes, as well as with the use of suction and

measurements of the clots. 1 g blood weight was converted to 1 mL blood volume.

3.4 Data Analysis

Data were entered and analysed with SPSS (version 25). Data obtained from quantitative variables like age, height, weight, BMI, GA, D, IOBL, OBL, and TMBL were given in mean ± SD if normally distributed and median (interquartile range) if not normally distributed. Qualitative variables such as parity and indication of cesarean section was summarized by means of frequencies and percentages. Baseline characteristics were compared between the two treatment groups to evaluate the comparability of the groups. The independent-samples t-test was used to compare mean intraoperative blood loss, 24-hour postoperative blood loss and total blood loss between Group A and Group B. The Mann-Whitney U test was to be planned for variables which had not been found to be normally distributed. Stratified analysis was conducted to consider the effects of potential modifying variables such as age, BMI, gestational age, parity, indication for cesarean section and operative duration. The p-value was considered statistically significant when < 0.05.

3. Results

There were 60 women with cesarean section (30 in each group). The background demographic and obstetric data were similar for both groups. The mean age was 28.4 ± 4.2 years in Group A and 27.9 ± 4.5 years in Group B. Mean gestational age was 38.2 ± 1.1 weeks and 38.5 ± 1.0 weeks, respectively, while mean BMI was 25.1 ± 2.8 kg/m² in Group A and 24.8 ± 3.1 kg/m² in Group B. There were no significant differences in these baseline variables.

Table 1. The baseline demographic data were compared.

Variable	Group A: Oxytocin Alone (n=30)	Group B: Oxytocin + Misoprostol (n=30)	p-value
Age (years)	28.4 ± 4.2	27.9 ± 4.5	>0.05
BMI (kg/m ²)	25.1 ± 2.8	24.8 ± 3.1	>0.05
Gestational age (weeks)	38.2 ± 1.1	38.5 ± 1.0	>0.05

Age, BMI and gestational age were similar between the two treatment groups. Adequate demographic homogeneity between groups was found as no baseline differences were found that were statistically significant.

Table 2. Comparison of Intraoperative Blood Loss

Variable	Group A: Oxytocin Alone (n=30)	Group B: Oxytocin + Misoprostol (n=30)	p-value
Intraoperative blood loss (mL)	380.5 ± 45.2	310.2 ± 38.6	<0.05

The combined-therapy group had less mean blood loss during surgery than the oxytocin-alone group. This difference was statistically significant, indicating reduced blood loss during surgery when using an intrauterine misoprostol.

Table 3. Blood loss measured the day after the surgery (24 hours) was compared.

Variable	Group A: Oxytocin Alone (n=30)	Group B: Oxytocin + Misoprostol (n=30)	p-value
24-hour postoperative blood loss (mL)	145.2 ± 22.1	112.4 ± 18.3	<0.05

Woman undergoing combined oxytocin and misoprostol had significantly reduced blood loss during their first 24 hours postoperative. Results reveal a continued decrease in observed blood loss after surgery.

Table 4. This is a comparison of Total Measured Blood Loss

Variable	Group A: Oxytocin Alone (n=30)	Group B: Oxytocin + Misoprostol (n=30)	p-value
Total measured blood loss (mL)	525.7 ± 52.4	422.6 ± 43.1	<0.001

Perioperative blood loss was significantly less in the combined-treatment group. There was a statistically significant difference between the two groups with Group B having slightly less measured blood loss (approximately 103 mL).

4.DISCUSSION

Postpartum hemorrhage (PPH) is still a major source of maternal morbidity and mortality, and is especially significant during cesarean section (C/S) when the amount of blood loss can be significant. Uterine atony is one of the common causes of postpartum bleeding and effective uterotonic therapy is an important aspect of obstetric treatment. It is also crucial to accurately estimate blood loss as visual assessment may not be accurate [1]. In addition, there is epidemiological evidence that a number of obstetric and maternal conditions can be associated with PPH and for this reason, delivery preventive measures are important [2].

The anti-prolapse drug of choice is oxycodone as it has been demonstrated to be effective and rapidly acting as an anti-prolapse (uterotonic) agent. But

other uterotonics might be needed if the uterus is not contracting well. Intravenous oxytocin or intrauterine misoprostol has been proven to be effective during cesarean delivery as uterotonics and both are recommended as uterotonics to prevent PPH [3]. However, evidence from systematic reviews has also demonstrated that the route of administration might also play a role when deciding whether or not to use oxytocin for PPH prophylaxis, as intravenous oxytocin remains a viable arm for PPH prevention [4].

Intrauterine use of misoprostol in the present randomized controlled trial was correlated with significantly less blood loss than was intravenous use of oxytocin alone. The mean blood loss did not differ between the two groups, but was 310.2 ± 38.6 mL for those receiving misoprostol plus oxytocin, compared to 380.5 ± 45.2 mL for those

who received only oxytocin (mean difference 70.3 mL, $p < 0.05$). Similarly, the mean blood loss during the first 24 hours after surgery was 112.4 ± 18.3 mL for the first group and 145.2 ± 22.1 mL for the second group with a mean difference of 32.8 mL ($p < 0.05$). Results of these trials were similar to the previous trials of misoprostol in regimens to reduce bleeding after cesarean section [5].

The findings of the present study are also in line with the results of the observation data administration of oxytocin only and misoprostol and oxytocin. In those who given both misoprostol and oxytocin, numfor et al reported better results in preventing postpartum bleeding than those receiving only oxytocin [6]. The findings from this study cannot be directly compared to the retrospective study, but do provide support for the potential benefits of the use of uterotonics of varying pharmacologic effects.

The evidence on intrauterine misoprostol is more relevant to this study. El-Hammroni et al. in their work about intrauterine misoprostol use during cesarean section found that the use of intrauterine misoprostol is a useful practice in preventing primary PPH [7]. The findings of Alalfy et al. are even more directly comparable to the current study because it was a randomized controlled study which compared intrauterine misoprostol with oxytocin in elective cesarean section to the use of oxytocin alone. In the combined treatment group they had significantly less blood loss, lower PPH rates and lower transfusion and uterotonics requirements [8]. The study they are doing is therefore a good comparison of the reduction in bleeding that we saw in our trial.

The present results are supported by the conclusions of Maged et al's systematic review and meta-analysis. They found misoprostol-containing regimens to be correlated with reduced intraoperative and postoperative blood loss and reduced the requirement for other uterotonics in cesarean delivery through their analysis of the randomized trials [9]. The authors also noted that there was also a lot of variation in dosage, route and timing of misoprostol use across the studies. This reduction in intraoperative blood loss (70.3mL) and total measured blood loss

(103.1mL) observed in the present study is consistent with the direction of effect observed in the general literature.

The selection of dosage is one of the crucial concerns when using misoprostol. In the current study, the dose of 400 µg of intrauterine misoprostol was given after delivery of the placenta. Sringamwong et al. when compared the use of 400mcg, 600mcg and 800mcg of intrauterine misoprostol with the use of oxytocin for cesarean delivery. As the dose increased, bleeding during surgery decreased but there was no significant difference in the amount of blood loss between the groups and PPH. The authors decided to use a dose of 400 µg as a reasonable dose since it was shown to have a preventive effect with relatively low dose-related adverse effects [10]. This dose chosen for this study is in agreement with these studies.

It is also important to consider the reduction in blood loss with the regimen of oxytocin. Phung et al. found differences in how IV oxytocin was administered to prevent PPH following cesarean delivery, and highlighted the importance of considering the dose and dosing strategy when interpreting their findings [11]. Since the same dose of oxytocin was used in the present trial in both groups, this helps avoid drawing conclusions about the difference between groups based on their exposure to oxytocin. The only difference between the two groups in the study was the women in one group received intrauterine misoprostol.

There is not a uniform amount of evidence of combinations of uterotonic agents. Jaffer et al. performed a network meta-analysis of uterotonic agents to prevent PPH after cesarean delivery, which showed that there was significant heterogeneity between the agents. In no comparisons did they find their group to be superior in the amount of estimated blood loss they experienced, and they were not sure in a few comparisons [12]. This is in contrast to the substantial decrease observed in the current trial, indicating that the effect of the treatment may vary depending on the study population, dosage, route, timing and clinical setting. In the present results, therefore, only this particular randomized

comparison can be considered, and findings are not necessarily indicative of the superiority of combination therapy over oxytocin in general. Safety and tolerability is another one of the parameters of choice in selecting uterotonic therapy. However, one systematic review [13] recognized that misoprostol could potentially have adverse effects and that there were variations in efficacy and adverse effect profile between misoprostol and oxytocin. Additional evidence for testing the effectiveness of oxytocin has also shown the potential adverse effect on the management and prevention of PPH [14]. While the present study showed that combination therapy had less blood loss, it is critical to assess risk of adverse effects in evaluating overall clinical usefulness of intrauterine misoprostol.

The variation in the results of the studies might also be due to the method of administration. In the case of cesarean delivery, Albazee et al. compared the effects of misoprostol with IV oxytocin and showed that the treatment effect varies between these two routes of administration in the rectum vs. IV [15]. These findings apply to the intrauterine route and may only be generalizable to other intrauterine misoprostol regimens similar to that used in the present study, and not intrauterine regimens of other misoprostol delivery systems, (e.g., oral, sublingual, or rectal).

Misoprostol is also known to possess uterotonic properties, from its use in other obstetric settings. Sambo et al. [16] compared the effects of intramuscular oxytocin and oral misoprostol on outcomes such as blood loss during active management of third stage of labour. However, in this study, the women used were those that gave birth naturally, not by cesarean section. It does not thus constitute evidence in the present trial, but it has to be considered a supportive pharmacological treatment.

An injection of oxytocin could also affect the amount of bleeding in the mother after giving birth. Torloni et al. did a systematic review and meta-analysis of the topic and concluded that time is an important factor when using oxytocin as a prophylactic uterotonic for PPH [17]. Similarly, Gök and Kaleli studied the time of oxytocin

administration during cesarean section and reported that the time of administration may affect the postpartum hemorrhage [18]. Neonates of both treatment groups were receiving the same IV treatment of oxytocin. The uniform administration will make the comparison more accurate as there will be no difference in the time of administering oxytocin between the groups.

Randomized trials have also been done in various obstetric populations with the use of the combination of misoprostol and oxytocin. Ottun et al. showed that misoprostol plus oxytocin was not necessarily correlated with reducing blood loss (as clinically defined as [PPH]) but correlated with variation in blood loss outcome when compared to oxytocin alone in the active management of 3rd stage of labour [19]. This was important for this study because the study primary outcome was the objective blood loss and not number of patients with known clinically PPH.

It has also been previously tried on as an additional agent in the delivery of cesarean section to oxytocin. Furthermore, Chaudhuri and Majumdar have shown that misoprostol can be sublingually given to reduce the bleeding during PPH in women who are at risk of developing PPH [20]. The present trial did not go through the intrauterine route of administration, but rather through the sublingual route – the same route as their study. Thus, the findings of the present study offer evidence specifically on the use of misoprostol (intrauterine use) in combination with intravenous oxytocin.

In conclusion, the present randomized controlled trial showed that women who were administered 400 µg of intrauterine misoprostol along with intravenous oxytocin experienced significantly less intraoperative, 24-hour postoperative and total measured blood loss than did women receiving intravenous oxytocin alone. Although there was a similar reduction in total blood loss in both groups, the mean was 103.1 mL, and the baseline demographic and obstetric parameters were similar. The findings are similar to those of a number of earlier investigations into the use of misoprostol-linked procedures in cesarean section, particularly when misoprostol is given as an intrauterine device. However, do note that the

absolute treatment effect needs to be compared, as there are large variations in the dose, route and timing of the treatment, patient characteristics and definition of PPH in previous studies.

There are a few limitations of the study. The generalizability of the findings may be limited due to relatively small sample size and the trial done in one institution. Maternal outcome was only measured during the first 24 hours after surgery, while no measurement of later maternal outcomes was made. The primary objective of the study was to compare blood loss and the study lacked the data to draw any conclusions between the groups regarding transfusion requirements, severe PPH, surgical technique or complications. Therefore, multicenter, randomized controlled trials using the same standardized approach to measuring blood loss and clinically important maternal outcomes are warranted. The present results, however, suggest that the use of intrauterine misoprostol with intravenous oxytocin may help to minimize blood loss in the peri-operative period when performing cesarean section.

Postpartum haemorrhage is a significant cause of morbidity and mortality particularly in operative deliveries. The new trend is to focus on the objective estimation of blood loss after pregnancy and appropriate prevention and management [1,3]. For cesarean section, oxytocin has been proven to be the first line uterotonic agent for preventing PPH and other uterotonics may be administered if uterine contraction is inadequate [4].

The women who received intrauterine misoprostol and intravenous oxytocin had less blood loss during surgery than those who only received intravenous oxytocin ($310.2 \text{ mL} \pm 38.6$ vs $380.5 \text{ mL} \pm 45.2$; $p < 0.05$). A similar reduction was observed in 24-hour postoperative blood loss (112.4 ± 18.3 vs. $145.2 \pm 22.1 \text{ mL}$; $p < 0.05$). Therefore, blood lost in total was significantly reduced in the combined treatment group (422.6 ± 43.1 vs. $525.7 \pm 52.4 \text{ mL}$; $p < 0.001$). The results of the present study suggest that there is an association between peroperative blood loss measured and use of adjunctive intrauterine misoprostol.

The results are similar to previous studies that assessed misoprostol as an addition to oxytocin for cesarean section. Randomized trials suggested that misoprostol with oxytocin might lead to fewer hemorrhage-related outcomes and fewer additional uterotonics given when compared to oxytocin alone [6] (depending on the route of misoprostol's administration). In another meta-analysis, it was seen that misoprostol-based regimen also decreased the blood loss in elective cesarean delivery [7]. Based on these data, misoprostol can be evaluated as an adjunctive drug for cesarean delivery, on a biological and clinical basis.

More recently, intrauterine administration has been investigated, too. Based on this, Masoumzadeh et al. randomly assigned 240 women for cesarean section to the combination of intrauterine misoprostol and oxytocin and compared it to other uterotonic regimens. They demonstrated that there were some differences between various routes of misoprostol and various regimens of oxytocin on blood loss in the perioperative period [8]. This underscores the need for this type of evaluation when interpreting misoprostol studies and when thinking about how the drug is used on such a specific route.

However, overall, literature should be treated with care. Two individual-participant-data meta-analyses of randomized trials comparing misoprostol to oxytocin indicated that there was no apparent difference between the two for the prevention of PPH, and some studies suggested methodological limitations and/or heterogeneity [9]. Others reported negative effects such as shivering, pyrexia, nausea and rise of body temperature with misoprostol [5]. So, the efficacy in reducing the blood loss observed in the current trial should be interpreted in the context of the trial size, single center design, intrauterine dose and administration protocol.

Overall, the findings of the study suggest that intrauterine misoprostol when used in combination with intravenous oxytocin can reduce blood loss during cesarean section in the early and intraoperative period. More RCTs with larger numbers of centers and with uniform methods to measure blood loss and to assess

adverse outcomes are needed to further confirm the efficacy and safety of this treatment.

5.CONCLUSION

The current randomized controlled trial showed that intrauterine misoprostol, 400 µg, when added to intravenous oxytocin, resulted in a significant decrease in the amount of blood loss in women undergoing LSCS. The mean intraoperative blood loss was less in the combined-treatment group and the same decrease in blood loss was seen during the first 24 postoperative hours. Thus, the amount of blood loss that was measured was significantly less in the women who were given intrauterine misoprostol and oxytocin compared to those who were given oxytocin alone. The findings reveal that using intrauterine misoprostol as an adjunctive uterotonic technique in cesarean section is one of the promising methods for reducing excessive blood loss particularly in areas where blood loss is a concern. The number of patients and single center design need to be considered in the interpretation of the results, however. The results obtained in this study are therefore only representative of this study population and not proof of superiority. Systematic assessment of adverse effects, transfusion requirements, rescue uterotonics and clinically important PPH should be considered in larger, well powered multicenter RCTs to further define the effectiveness and safety of this combination.

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