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COMPARISON OF THE EFFECTS OF PREOPERATIVE AND POSTOPERATIVE SUBLINGUAL MISOPROSTOL IN THE TREATMENT OF POSTARTUM BLEEDING PREVENTION

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ABSTRACT

Background: Postpartum haemorrhage is generally defined as blood loss exceeding 500 milliliters after vaginal delivery and 1000 ml after cesarean section. The most commonly used drugs in the management of PPH are uterotonic agents including misoprostol.

Methods: This study is a quasi-experimental prospective study with a clinical trial design that compares the efficacy of misoprostol 400 mcg given preoperatively and postoperatively in the September 2020 period until the number of samples is fulfilled as many as 54 subjects.

Results: There were statistically significant differences in the amount of blood from gauze, the amount of blood from suction, intra-operative bleeding, post-operative bleeding, and total bleeding ($p<0.05$) but there was no significant difference in the amount of gauze used.($p> 0.05$) There was no statistically significant difference in the secondary outcomes (fever, chills, and nausea and vomiting) which was statistically significant in the two groups ($p=1.00$) There was a difference in the mean pre-operative and post-operative hemoglobin and hematocrit levels between the two treatment groups ($p<0.001$ and $p=0.002$).

Conclusion: There is a difference in the mean difference between hemoglobin and hematocrit between pre-operative and post-operative hemoglobin and hematocrit in the two treatment groups.

Keywords: misoprostol, sublingual, preoperative, postoperative, caesarean section

INTRODUCTION

Postpartum haemorrhage (PPH) is generally defined as blood loss exceeding 500 milliliters (Ml) after vaginal delivery and 1000 Ml after cesarean section (SC). PPH is often classified as primary/immediate/early, which occurs within 24 hours of birth, or secondary/delayed/late, which occurs more than 24 hours to 12 weeks postpartum.[1] PPH is the leading cause of maternal mortality and morbidity worldwide and accounts for nearly a quarter of all pregnancy-related deaths. Many of the deaths associated with PPH can be prevented by prompt diagnosis and more timely and aggressive management. The morbidity from PPH can be severe with sequelae including organ failure, shock, edema, compartment syndrome, transfusion complications, thrombosis, acute respiratory distress syndrome, sepsis, anemia, intensive care, and prolonged hospitalization.[2]

The overall prevalence of PPH worldwide is estimated at 6–11% of births with variations across regions. There has been an increase in PPP in developed countries, including the United States, Canada, Australia, Ireland, and Norway, since the 1990s. In the United States, one study found that the incidence of PPH increased by 26% from 1994-2006 (2.3% vs. 2.9%, respectively).[3] The most common etiology of PPH is

uterine atony, occurring in about 80 percent of cases. Atony may result from uterine overdistention, infection, placental abnormalities, or bladder distension. PPH interventions generally evolve from compression techniques, medications and surgery.[4] Conservative management techniques such as uterotonic drugs, which cause the uterus to contract, external uterine compression, and bimanual compression are commonly used as "first line" management. The most common drugs used in the management of PPH are uterotonic agents. These include oxytocin, misoprostol , methylergonovine maleate, carboprost tromethamine and dinoprostone.[5]

Misoprostol is a synthetic prostaglandin E1 analogue, which is commonly used for the prevention and management of PPH; has strong uterotonic properties and fewer side effects at therapeutic doses; absorbed orally, vaginally, rectally or oral mucosa. Misoprostol is affordable, widely available, and easy to administer via multiple routes, and has a good safety profile if administered and monitored properly, all of which may make it the standard treatment choice for PPH. Benefits (cervical dilatation and uterine contractions) and side effects (nausea, vomiting, diarrhea, fever, and chills) are dose dependent. According to this study, the oral route had the fastest absorption, but the shortest duration. The rectal route has slow absorption but long duration. The buccal and sublingual routes have rapid absorption, long duration and the greatest total bioavailability.[6]

Previous studies have shown that misoprostol is effective in reducing blood loss during and after CS regardless of route of administration. However, the optimal timing for administration of misoprostol to reduce the amount of PPH is still under discussion. One study found that preoperative administration of sublingual misoprostol (400 mg) during CS was superior to postoperative administration because it was associated with reduced intraoperative and postoperative blood loss and decreased hemoglobin levels.[6] From the description above, the authors want to conduct research on the differences in the therapeutic effects of misoprostol given sublingually during preoperative and postoperative CS for the prevention of postpartum hemorrhage.

METHODS

This study is a prospective quasi-experimental study with a clinical trial design comparing the efficacy of misoprostol 400 mcg given preoperatively and postoperatively. The study was conducted at the Department of Obstetrics and Gynecology at the Haji Adam Malik General Hospital Medan and Sundari Hospital in the period September 2020 until the number of samples was met, where the population was all patients who underwent elective sectio caesaria at Haji Adam Malik Hospital Medan and Sundari Hospital in the period September 2020 until the number of samples is fulfilled as many as 54 subjects consisting of 27 subjects in each group receiving pre-operative misoprostol and post-operative misoprostol administration. Samples were taken from the population that met the inclusion and exclusion criteria who would undergo elective cesarean section surgery. After statistically calculated, all samples were randomly divided into 2 groups. Group A received 400 mcg sublingual misoprostol before surgery, while group B received 400 mcg sublingual misoprostol after surgery.

All patients who underwent elective caesarean section at the Haji Adam Malik General Hospital Medan and North Sumatra University Hospital for the September 2020 period until the number of samples was met. The sampling technique used is the consecutive sampling technique. Consecutive side is a sampling technique in which all subjects who come and meet the selection criteria are included in the study until the number of subjects is met.

The inclusion criteria in this study were pregnant women at term with a single fetus, elective caesarean section with lower uterine segment incision and spinal anesthesia, preoperative and postoperative hemoglobin and hematocrit data, pregnant women who were willing to participate in the study and pregnant women without blood clotting disorders. While the exclusion criteria in this study were patients who were taking anticoagulants, experienced antepartum bleeding and pregnant women with placenta previa.

Univariate and bivariate analysis will be presented in the form of tables, graphs and narratives, to determine the frequency distribution based on the characteristics of the research subjects. Categorical data is presented in the form of frequency n (%) and numerical data is presented in the form of mean±SD or Median (minimum-maximum). Bivariate analysis was used to determine the relationship between the independent variable and the dependent variable. Data analysis was performed to compare the preoperative and postoperative effects of misoprostol. The normality test used was the Saphiro Wilk test for the number of samples <50 and Kolmogorov Smirnov for the number of samples >50. The hypothesis test used is the independent T test if the data distribution is normal ($p > 0.05$), whereas if the data distribution is not normal, the Mann-Whitney test will be carried out.

RESULTS

The study found 54 subjects consisting of 27 subjects in each group receiving pre-operative misoprostol and post-operative misoprostol administration. Table 1 shows the basic characteristics of the

research subjects in the two groups, namely age, number of parity, and number of previous cesarean sections, which were not statistically significant.

Table 1 Characteristics of Research Subjects in Both Research Groups

	Misoprostol Administration Group Pre-Operation	Misoprostol Administration Group Post-Operation	*P-Value*
Age (years)	28.74 ± 6.97*	28.15 ± 6.78*	0.753[a]
Parity	2 (1-7)**	2 (1-9)**	0.710[b]
Previous history	SC1 (0-2)**	1 (0-2)**	0.881[b]

* Data is presented in Mean±SD
** Data is presented in Median (Min-Max)
a T-Independent Test
b Mann-Whitney test

Table 2 illustrates the difference in the amount of blood loss in the two groups. There were differences in the amount of blood from gauze ($p<0.01$), the amount of blood from suction, intra-operative bleeding, post-operative bleeding, and total bleeding which were very statistically significant in the two groups ($p<0.001$). There was a lower amount of blood from the gauze, the amount of bleeding on suction, intra-operative bleeding, post-operative bleeding, and total bleeding in the pre-operative misoprostol group than in the post-operative misoprostol group. There was a lower amount of gauze in the preoperative misoprostol group than in the postoperative misoprostol group, but this difference was not statistically significant ($p > 0.05$).

Table 2 Differences in Blood Loss in the Two Treatment Groups

	Misoprostol Administration Group Pre-Operation *	Misoprostol Administration Group Post-Operation *	*P Value*[a]
The amount of blood from the gauze	172.19 □ 64.58	243.13 □ 110.87	0.009
Amount of gauze	10.52 □ 3.03	11.56 □ 4.07	0.47
Amount of blood from suction	84.07 □ 49.4	247.77 □ 156.01	<0.001
Intra-operative bleeding	256.26 □ 83.67	490.91 □ 187.09	<0.001
Post-operative bleeding	99.03 □ 27.29	201.25 □ 113.55	<0.001
Total bleeding	335.30 □ 84.26	692.17 □ 187.59	<0.001

* Data is presented in mean±SD
a Mann-Whitney test

Table 3 describes the differences in the secondary outcomes of the two groups. There was no statistically significant difference in secondary outcomes in the two groups. Each of the four subjects in the preoperative misoprostol administration and postoperative misoprostol administration had fever, chills, and nausea and vomiting.

Table 3 Differences in Misoprostol Secondary Outcomes in the Two Treatment Groups

Variable	Misoprostol Administration Group Pre-Operation	Misoprostol Administration Group Post-Operation	*P Value**
Fever	4 (14.8%)	4 (14.8%)	1.00
Chills	4 (14.8%)	4 (14.8%)	1.00
Nausea and vomiting	4 (14.8%)	4 (14.8%)	1.00

**Fisher Exact test*

Table 4 depicts the difference in mean pre-operative and post-operative hemoglobin and hematocrit levels between the two treatment groups. It was found that postoperative hemoglobin and hematocrit levels were lower and statistically significant in both the preoperative misoprostol administration and the postoperative misoprostol administration group when compared to the preoperative hemoglobin and hematocrit levels in both groups ($p<0.001$ and $p=0.002$).

In comparison between groups, it was found that preoperative hemoglobin and hematocrit levels were lower in the preoperative misoprostol group than in the postoperative misoprostol group, but this difference was not statistically significant ($p=0.52$ and $p=0.29$). On the other hand, the postoperative hemoglobin and hematocrit levels were higher in the preoperative misoprostol group than the postoperative misoprostol group and this difference was not statistically significant ($p=0.71$ and $p=0.47$).

Table 4. Differences in Mean Hemoglobin Levels and Pre-operative and Post-operative Hematocrit between the Two Treatment Groups

	Misoprostol Administration Group Pre-Operation *			Misoprostol Administration Group Post-Operation *			*P Value* (comparison between group)[b]	
	Pre	Post	*P Value*[a]	Pre	Post	*P Value*[a]	Pre	Post
Hemoglobin level	10.58 ± 1.29	9.66 ± 1.13	<0.001	10.80 ± 1.27	9.52 ± 1.57	<0.001	0.52	0.71
Hematocrit level	33.70 ± 3.76	29.70 ± 2.99	<0.001	34.80 ± 3.85	28.97 ± 4.3	0.002	0.29	0.47

*Data is presented in mean ±SD
a. T-Pair Test
b.test T-Independent

Table 5 illustrates the difference in the mean difference between hemoglobin and hematocrit between pre-operative and post-operative hemoglobin and hematocrit in the two treatment groups. The mean difference in hemoglobin levels was lower in the preoperative misoprostol group than in the postoperative misoprostol group and statistically significant ($p<0.05$). In the preoperative misoprostol group, the mean difference in hematocrit levels was lower than the difference in hematocrit levels in the postoperative misoprostol group, but this difference was not statistically significant ($p>0.05$).

Table 5. Differences in the Mean Difference between Hemoglobin and Hematocrit in the Two Treatment Groups

	Misoprostol Administration Group Pre-Operation *	Misoprostol Administration Group Post-Operation*	*P Value*
Hemoglobin differences	0.91 □ 0.45	1.27 □ 0.70	0.03[a]
Hematocrit Difference	4.00 □ 2.44	5.83 □ 3.75	0.054[b]

** Data is presented in mean ±SD*
a. T-Independent test
b. Uji Mann-Whitney

DISCUSSIONS

Table 1 shows the distribution of characteristics of the research subjects in the two test groups. Characteristics of study subjects included mean age, parity, and number of previous SC history. The results showed that there were no statistically significant differences in all the characteristics of the research subjects in the two test groups. This is in accordance with the study conducted by Milhan, et al. The year 2019 mentions the variable age of women during pregnancy, and the number of parity does not have an impact on delivery by cesarean section or bleeding that occurs.[7]

This study is a prospective quasi-experimental study through clinical trials comparing the efficacy of misoprostol 400 mcg given pre-operatively and post-operatively sublingually in patients undergoing cesarean section at the Department of Obstetrics and Gynecology, Haji Adam Malik General Hospital Medan and General Hospital. University of North Sumatra in the period September 2020 until the number of samples is met.

Table 2. This study shows statistically significant differences between the two test groups in the amount of blood from the gauze, the amount of blood from suction, intra-operative bleeding, post-operative bleeding, and total bleeding ($p<0.001$). Where the amount of total bleeding was found to be less in the preoperative misoprostol group than the postoperative misoprostol administration. This study is in accordance with research by Youssef, et al. in 2019 which also compared the effect of preoperative and postoperative sublingual misoprostol (400 mcg) in reducing the amount of blood loss during and 24 hours after cesarean section to determine the optimal time for drug administration. They found that sublingual misoprostol administration significantly reduced intraoperative and postoperative blood loss when administered preoperatively.[6]

The study comparing the efficacy of misoprostol in pre-operative and post-operative patients who will undergo cesarean section by Ragab et al in 2015 where in their study, 400 mcg of misoprostol given rectally before surgery was more effective in reducing blood loss during elective cesarean section than given after operation.[7] Correspondingly, the study by Omozuwa, et al. 2006 also concluded that sublingual misoprostol 600 mcg was more effective in preventing intra-operative bleeding than rectal administration.[8]

In another study by Vimala, et al. In 2006 in India, significantly lower blood loss was found in the sublingual misoprostol group compared to the oxytocin group (819 ml vs 974 ml; $p=0.004$).[8] A study by Sood et al in 2012 showed that mean intra-operative blood loss was significantly less in the sublingual misoprostol group (400 mcg) compared to the placebo group (595±108 vs 651±118 ml, p= 0,*025*).[9] Research by Lapare, et

al. 2006 in Switzerland, stated that no statistical difference was found in blood loss between the misoprostol and oxytocin groups, but less blood loss in the misoprostol group.[10]

In the variable amount of gauze, there was no significant difference between the two groups (p>0.47). The use of gauze as a method of measuring blood loss is a quantitative technique and is commonly used in surgery by measuring the weight of all the gauze used. However, studies conducted by Youssef, et al, Ragab, et al, Vimala, et al, Sood, et al, Milhan, et al, and Omozowa, et al. regarding the use of sublingual misoprostol in preventing bleeding in cesarean section surgery does not explicitly mention the amount of gauze used, but grouping it in a complete unit the total amount of blood loss that occurs so that this allows the variable amount of gauze to not differ significantly.

According to several studies, the oral route has the fastest absorption, but the shortest duration. The rectal route has slow absorption but long duration. The buccal and sublingual routes have fast absorption, long duration and the greatest total bioavailability.[6] The absorption rate of misoprostol was found to be faster when administered orally with reaching maximal concentrations after 12 minutes with a half-life of 20-30 minutes. The rectal and vaginal routes have slower absorption rates and lower maximal concentrations after 60 minutes, leading to sustained side effects. In addition, slower absorption leads to lower concentration levels and consequently reduced side effects compared to the sublingual route.[11,12]

The sublingual route avoids discomfort and fecal contamination compared to the rectal route, which cannot be performed during cesarean section. In India and Guinea Bissau, the advantages of sublingual misoprostol have been explored with trained nurses in rural areas to administer misoprostol after vaginal delivery and this has resulted in a significant reduction in the number of patients referred to tertiary centers for postpartum hemorrhage.[13] However, a 2014 study by Abd-Ellah using sublingual misoprostol 600 mcg concluded that it could cause higher drug side effects and complications due to increasing the dose.[14] Leon, et al. in 2012 stated that administration of 800 mcg of sublingual misoprostol had side effects of chills and hyperpyrexia (body temperature reached 40°C) in 36% of subjects.[15]

According to table 3. there is no significant difference between the two groups. Some secondary outcomes that often arise from the administration of misoprostol are fever, nausea, vomiting, and diarrhea. In our study, there was no statistically significant difference in secondary outcomes between the two groups (p = 1.00). Each of the four subjects in the preoperative misoprostol administration and postoperative misoprostol administration group experienced fever, chills, nausea, and vomiting. This is in line with the study by Youssef, et al. in 2019 where fever and chills were more common in group 1 than group 2 with a statistically significant difference (p = 0.036 and p = 0.002). Rates of nausea, vomiting, and diarrhea were similar in the two groups. Occurrence of gastrointestinal symptoms, and headache was similar in both groups.[6] Misoprostol in the study of Owonikoko, et al. 2011 was also associated with secondary side effects (fever and chills), and was not life-threatening. Other studies have also reported complaints of bad taste, nausea, vomiting and diarrhea with the use of misoprostol. According to him, these secondary side effects do not affect the overall safety of misoprostol. The occurrence of blood loss also cannot be attributed to the effectiveness of misoprostol as a uterotonic agent, but it does emphasize the need for an experienced hand in cesarean section.[16]

In the study of Kumari, et al. in 2016 they compared misoprostol vs placebo in the reduction of intra-operative and post-operative blood loss. Misoprostol is administered rectally after catheter insertion before spinal anesthesia; the dose of misoprostol is 200 mcg. Side effects were found to be slightly higher in the misoprostol group (20%) than in the placebo group (14%) although not statistically significant (p=0.25).[17] In the 2012 Elsedeek study, only 24 of 400 participants complained of postpartum fever, with no significant difference between the two groups. In Sood Atul, et al. In 2012 there was an increase in the incidence of shivering subjects. However, no differences in fever, nausea or vomiting, or anything similar have been reported in other literature.[18,19]

Table 4 describes the difference in the mean levels of hemoglobin (Hb) and hematocrit (Ht) pre-operatively and post-operatively between the two groups. There is a significant difference between hemoglobin and hematocrit in each test group, but there is no significant difference in hematocrit and hematocrit levels in the comparison of the two groups. Table 5 shows a significant difference in the mean difference between hemoglobin and hematocrit between the two groups, where preoperative misoprostol administration had a lower hemoglobin and hematocrit difference than postoperative administration ($p < 0.05$).

Ragab, et al. in 2016 stated that post-operative hemoglobin values were significantly lower in group 2 (administration of misoprostol after surgery) than group 1 (p<0.001). Three women in group 2 (1.7%) had an estimated blood loss of more than 1000 m; however, none of them required blood transfusion as all were hemodynamically stable, although one patient had the lowest postoperative hemoglobin value (85.6 g/L).[20] Furthermore, the study of Ahmad, et al. 2014 showed a significant decrease in pre-operative Hb in the misoprostol group (0.87±0.29 vs 1.01±0.26g, p = 0.0018), and a significant post-operative hemoglobin level (24 hours) lower in the group given postoperative rectal misoprostol, (9.8±1.24) than the group given

preoperative misoprostol (10.5±1.31) with a value (p=0.034).[21] In Sood Atul et al. in 2012 the mean postoperative hemoglobin was significantly higher in the misoprostol group than in the placebo group (9.79±0.99 vs 9.51±0.56, p=0,*023*).[22]

The study by Kumari, et al. In 2016, the hematocrit level was lower in the group given misoprostol than the control group (p=0.006).[23] Contrary to research by Youssef, et al. in 2019 regarding preoperative and postoperative administration of sublingual misoprostol in cesarean section patients, which concluded that hematocrit and hemoglobin were found to be higher in the first group (sublingual misoprostol was given preoperatively) than the second group (p = 0.07 and p = 0.04).[6]

Clinical trials regarding the efficacy of sublingual misoprostol before and after cesarean section have not been widely reported. Two studies by Youssef et al. in 2019 and Ragab, et al. previously concluded that pre-operative administration of 400 mg of misoprostol via sublingual and rectal administration provides better benefits than post-operative administration. This was associated with the total amount of bleeding and the hemoglobin level that occurred, although side effects such as fever and chills at these doses did occur. Likewise, this study obtained appropriate results, and is expected to be a reference for further research, although there are some limitations. The limitation of this research is the limited number of samples. So it is suggested for the next research to be carried out with a multi-centered study with a more detailed approach to the characteristics of the subject.

The weakness in this study is that the researcher did not divide the classification system for calculating the amount of bleeding based on the baby's weight, history of cesarean section, equal level of operator expertise in performing the procedure, and intraoperative findings such as incision area and duration of placental expulsion until complete delivery. However, the results of this study can be taken as a benchmark and reference for future research considering the classification system and other divisions are quite detailed in calculating the amount of bleeding that represents the effect of misoprostol.

CONCLUSION

Based on the data on the basic characteristics of the research subjects in the two groups, the results were not statistically significant. (p>0.05) There was a statistically significant difference in the amount of blood from gauze, the amount of blood from suction, intra-operative bleeding, post-operative bleeding, and total bleeding (p<0.05) but there was no significant difference in the amount of gauze used. (p>0.05) There was no statistically significant difference in the secondary outcomes (fever, chills, and nausea and vomiting) which was statistically significant in the two groups (p=1.00) There was a difference in the mean pre-operative and pre-operative hemoglobin and hematocrit levels. postoperatively between the two treatment groups (p<0.001 and p=0.002). There was a difference in the mean difference between hemoglobin and hematocrit between pre-operative and post-operative hemoglobin and hematocrit in the two treatment groups. (p=0.03 and p=*0.05).*

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