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ORIGINAL ARTICLE

Preoperative versus Postoperative Sublingual Misoprostol in Reducing Blood Loss during and after Primary Elective Cesarean Section

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ABSTRACT:

Background: One of the major risks associated with cesarean sections (CS) is blood loss. According to earlier studies, misoprostol effectively lowers intraoperative blood loss during caesarian sections and in the primary postpartum period regardless of how it is taken. However, the best time of administration of misoprostol to decrease blood loss is still under discussion. This study aimed to compare the effect of preoperative vs. postoperative administration of 400µg sublingual misoprostol in decreasing blood loss both intraoperative and 24 hours postoperative.

Methods: These randomized clinical trials study conducted at Zagazig university hospitals. Including two groups of patients scheduled for elective primary caesarian delivery each group includes 34 patients, group one was instructed to administer 400ug misoprostol sublingually preoperatively and the other group postoperatively. All patients were subjected to full clinical examination including Obstetric ultrasonography.

Results: The intraoperative blood loss in group 2 was 426.5±6.2ml, compared to 395.1±4.1ml in group 1, and the 24-hour postoperative blood loss was 85.4±8.6ml s. 62.3±91ml, respectively. Significant difference ($P < 0.05$) between the two investigated groups in hemoglobin and HCT postoperatively, with the preoperative sublingual group having higher levels than the postoperative group. Hemoglobin and HCT levels before and after treatment did not, however, differ statistically significantly.

Conclusions: Although fever and chills could still occur, preoperative administration of sublingual misoprostol (400µg) during CS is preferable to postoperative administration since it is linked to less intraoperative and postoperative blood loss and a lower decline in hemoglobin levels.

Keywords: Blood loss; Cesarean Section; Misoprostol.

INTRODUCTION

One of the most common surgical procedures performed globally is the cesarean section (CS) [1]. The Cesarean section is in increasing each year throughout the world with incidence ranging from 20-30% [2]. Primary postpartum hemorrhage (PPH) is one of the major complications that can occur after a cesarean delivery for both the mother and the fetus.

Primary PPH is the leading cause of maternal death globally and is defined as a blood loss of over 1000 milliliters within the first 24 hours following birth [3].Maternal mortality and morbidity are primarily caused by primary postpartum hemorrhage [4]. About 25% of maternal deaths are caused by it, and 12% of cases result in severe anemia [5].

In the cesarean section, oxytocin is the common uterotonic used to prevent atony of the uterus and postpartum bleeding, but in many cases (10-40%) additional ecbolics are needed to have effective uterine contraction to prevent bleeding [6]. A previous Cochrane review

showed that combination of oxytocin with misoprostol is one of the strong effective combinations in decreasing postpartum hemorrhage better than using oxytocin alone [7].

In the realm of obstetrics, misoprostol, a synthetic prostaglandin E1 analog, is frequently used to prevent and manage postpartum hemorrhage. It has strong uterotonic effects and few side effects if used in low doses [8]; it is absorbed in many routes orally, rectally and across the oral cavity, highly affordable, available, and safe if properly used, which makes it good option for managing PPH in low-resource setting [9]. The effects and the side effects of misoprostol increase with increasing its dose [10].

Synthetic (PGE1) is more stable than naturally occurring prostaglandins at room temperature, after absorption it turned to active drug misoprostol acid, binding to E prostanoid receptor 3 (EP-3), increasing calcium mobilization leading to uterine contraction by actin myosin contractility [11].

Misoprostol has many uses in the obstetrics and gynecology field; it can be used in miscarriage and abortions [12]. It also has an efficient role in managing atonic postpartum bleeding. It can also be used in inducing cervical ripening and softening before gynecological procedure resulting in less pain during instrumental passage in these procedures [13].

According to previous studies, the buccal and sublingual routes offer the highest overall bioavailability, the longest duration, and the fastest absorption [14]. Given that CS causes twice as much blood loss as vaginal delivery, blood loss is one of the major side effects of CS [15].

The ideal timing to use misoprostol to reduce the quantity of PPH is still up for debate, however prior investigations have demonstrated that it is beneficial in minimizing blood loss during and after cesarean birth [16]. The aim of this study was to compare the effect of preoperative vs. postoperative administration of 400 µg sublingual misoprostol in decreasing blood loss both intraoperative and 24 hours postoperative.

METHODS

This randomized clinical trial study was conducted on sixty-eight pregnant women who would undergo cesarean section under spinal anesthesia at the attending Zagazig University Hospitals during the period from February 2023 to August 2023. The included women were divided into two groups, each group including 34 patients. One group was instructed to administer 400 µg misoprostol sublingually preoperatively and the other group postoperatively. Exclusion Criteria were anemia Hb<9gm/dl, Multiple gestations, Polyhydramnios, Antepartum hemorrhage, women undergoing anticoagulant treatment, having thrombocytopenia, or having known coagulopathies.

Women who have a history of severe heart disease, hypertension that needs to be treated, or liver, kidney, vascular, or endocrine problems. Women who suffer from severe asthma or any other serious allergy. Women with glaucoma or known hypersensitivity to misoprostol or other prostaglandins (PGs) are among those who should not get prostaglandins.

mental illness that makes it difficult for the patients to comprehend the purpose, extent, and potential outcomes of the study.

Every woman was asked to provide their whole medical history, including personal information. Comprehensive medical history, including obstetric history, past operations, and clinical examinations, including general, measurements (heart rate, respiration rate, weight, and regular obstetric examination), as well as a local and physical examination. Laboratory investigations: for the purpose of CBC assessment, a 3 ml blood sample was drawn from each subject in a tube containing EDTA while maintaining complete sterility. All patients had blood drawn two hours prior to and twenty-four hours following the CS. All patients undergo obstetric ultrasonography to confirm their gestational age. The sixty-eight

parturients were divided into two equal groups, with thirty-four cases in each group. An independent statistician created sealed opaque envelopes with a group assignment using a computer-generated random number table. A nurse who was not informed of the contents was given two groups of envelopes, which represented two research groups. The envelopes were distributed to patients at random by the nurse, who alternated between the groups. Patients in group 1 received 400µg sublingual misoprostol right before skin incision and after urine catheterization. Sublingual misoprostol was administered to patients in group 2 as soon as their skin was closed. Under the guidance of an assistant lecturer or obstetrician specialist, all the cesarean deliveries were done by me. Every patient received the identical cesarean delivery procedure. The procedure was carried out under spinal anesthesia. Within the shaved patch of pubic hair, which was approximately 10 to 12 cm long, the abdominal skin was incised using a Pfannenstiel incision 2 to 3 cm above the symphysis pubis. The rectus muscles were isolated and dissected from the longitudinally exposed peritoneum following the opening of the rectus fascia.

A transverse incision in the lower section was used to access the uterus. Following fetal delivery, 5 IU of oxytocin was slowly infused into each group. Absorbable continuous vicryl1 sutures were used to repair the uterine incision in two layers, and they were also used to suture the parietal peritoneum. Vicryl2 sutures were used continuously to seal the rectus sheath. Absorbable continuous vicryl1 sutures were used to close the subcutaneous fatty layer, and subcuticular sutures were used to seal vicryl2-0 on the skin. The weight difference between all of the towels before and after CS was computed. The suction apparatus's estimated intraoperative blood loss was measured in milliliters. During surgery, a nurse was tasked with collecting blood and amniotic fluid using two different suction sets. Additionally, all of the surgical towels used were the same size, weight, and weight every 1 gram, both before and after CS. Weight gain was equivalent to a 1-mL drop in blood volume. Blood loss in the suction device was added to the weight differential of used towels to determine the overall quantity of intraoperative blood loss. For the first 24 hours following surgery, a second nurse was in charge of weighing the soaked towels that were placed in the vulvar region in order to determine the external blood loss. The weight difference was then used to calculate it. The blood loss during and after surgery was computed. Twenty-four hours following surgery, a second blood sample was taken to look for variations in the Hb and Hct levels.

Postoperative follow up:

Prior to CS, on average during the procedure, and two hours after the procedure, the vital signs (baseline blood pressure and heart rate) were taken. In the postpartum ward, routine follow up for the blood loss vaginally and patient vital stability. Following placenta delivery, the surgeon calculated the volume of blood lost during CS using the standard method (visual estimates, number of used swabs, and amount of aspirated blood) and classified it as major (>1000 ml), moderate (500-1000 ml), and average (≤500 ml).

Calculation of the quantity of blood loss: more accurate

Estimated blood loss

$$= \text{EBV} \times \frac{\text{Preop hematocrit} - \text{Postop hematocrit}}{\text{Preop hematocrit}}$$

Where the woman's weight in kg×85 equals the estimated blood volume (EBV) in milliliters. Excessive bleeding during the procedure was defined as blood loss greater than 1000 milliliters. The amount of intraoperative blood loss after fetal birth was the main outcome. Blood loss of 1000 milliliters or more is known as postpartum hemorrhage (PPH). Hemoglobin decline within 24 hours after delivery was one of the secondary outcomes. Contraction of the uterus, need of uterine massage, fundal level compared to the umbilicus within a day, transfusions of blood and drug use adverse

effects (pyrexia, shivering, vomiting, and nausea).

Statistical Methods

Information gathered over time, a basic clinical assessment, microsoft Excel software was used to code, enter, and evaluate laboratory results and outcome measures. For analysis, the data were subsequently loaded into the Statistical Package for the Social Sciences (SPSS version 20.0) program. Qualitative data is represented by numbers and percentages, while quantitative data is represented by mean ± SD. The Chi square test (X2) was utilized to assess the significance of the differences and the correlation between the qualitative variables. t test or Mann Whitney differences between quantitative independent groups, Kappa agreement, and logistic regression predictors. For significant results, the P value was set at less than 0.05, and for very significant results, it was less than 0.001.

RESULTS

After 80 women were evaluated for eligibility, six were disqualified because they did not fit the requirements for inclusion, and seven of them declined to take part in the research is depicted in **Figure 1** of the study flowchart.Groups 1 and 2 are the preoperative and postoperative misoprostol groups, respectively. The two groups under study did not differ statistically significantly in terms of age, BMI, gravidity, parity, or gestational age. Regarding cesarean section indications, there was no statistically significant difference between the two groups under study (**Table 1)**.Demonstrated that table 2, two groups under study differed statistically significantly in terms of blood loss, with more blood loss occurring either intraoperatively, compared to group 1, group 2 experienced more postoperative and total blood loss.

Demonstrated table 3 that there was a statistically significant difference between the two groups under study in terms of hemoglobin and HCT after surgery, with group 1 having a greater level than group 2. However, in relation to HCT and preoperative hemoglobin, before and after therapy, there was no statistically significant difference.Table 4; showed that according to shivering, there was statistically difference between the two groups under investigation, with group 1 experiencing it more frequently than group 2, while there was no statistically significant difference in other side effects**.**

Table (1); Basic data of the studied groups (NO=68):

Variable	Group 1 No. (34)	Group 2 No. (34)	t-test	P
Age (years)				
mean ± SD	**29.7±4.9**	**31.3±6.1**	**1.19**	**0.2**
(range)	**(19-38)**	**(20-41)**		
BMI				
mean ± SD	**28.4±4.6**	**28.6±5.7**	**0.15**	**0.9**
(range)	**(20-34)**	**(19-36)**		
Gravidity				
mean ± SD	**2.8±1.3**	**2.6±1.2**	**0.65**	**0.5**
(range)	**(1-4)**	**(1-5)**		
Parity				
Nulliparous	**9 (26.5%)**	**7 (20.6%)**	**0.7**	**0.4**
Multiparous	**25 (73.5%)**	**27 (79.4%)**		
Gestational age (weeks)				
mean ± SD	**38.7±2.2**	**38.1±2.1**	**1.15**	**0.3**
(range)	**(37-40)**	**(37-40)**		

Variable	Group 1 No. (34)	Group 2 No. (34)	t-test	P
Indications of cesarean section	**Group 1 No. (34) NO. (%)**	**Group 2 No. (34) NO. (%)**	**χ^2**	**P-value**
Malpresentation	**8 (23.5%)**	**9 (26.47%)**	**1.4**	**0.91**
Postdate	**10 (29.4%)**	**9 (26.47%)**		
Oligohydraminos	**3 (8.7%)**	**4 (11.6%)**		
Elderly primigravida	**8 (23.5%)**	**7 (20.5%)**		
CPD	**3 (8.7%)**	**2 (5.8%)**		
Primary infertility	**2 (5.8%)**	**3 (8.7%)**		

Table (2); Mean and standard deviation of blood loss pre and post-operative in the two studied groups:

Blood loss	Group 1 No. (34)	Group 2 No. (34)	t-test	P
Intraoperative blood loss (ml) mean ± SD (range)	395.1±4.1 (365-415)	426.5±6.2 (380-450)	24.6	**0.0001****
Postoperative blood loss mean ± SD (range)	62.3±9.1 (40-75.8)	85.4±8.6 (67-100.2)	10.8	**0.0001****
Approximate total blood loss (ml) mean ± SD (range)	457.4±21.5 (405-490.2)	511.9±23.7 (447-550.5)	9.93	**0.0001****

Group 1 represents preoperative misoprostol group and group 2 represents postoperative misoprostol group. **Statistically highly significant difference ($P \leq 0.0001$).

Table (3); Mean and standard deviation of hemoglobin and HCT pre and post-operative in the two studied groups:

Mean hemoglobin	Group 1 No. (34)	Group 2 No. (34)	t-test	P
Preoperative hemoglobin mean ± SD (range)	12.1±2.5 (10-14.5)	11.8±2.1 (9.8-14.6)	0.54	0.6
Postoperative hemoglobin 24h mean ± SD (range)	10.9±0.7 (9.2-10.8)	9.8±0.8 (9.4-11.4)	6.03	**0.001***
Preoperative HCT mean ± SD (range)	33.88±2.3 (29.8-36.7)	33.77±2.8 (29.8-35.9)	0.18	0.86
Postoperative HCT 24h mean ± SD (range)	32.14±3.7 (26.2-33.8)	30.38±2.8 (28.4-35.4)	2.21	**0.03***

Group 1 represents preoperative misoprostol group and group 2 represent postoperative misoprostol group. *Statistically significant difference ($P \leq 0.05$).

Table (4); Comparison between the two studied groups as regard to side effects of drugs:

Side effects of drugs	Group 1 No. (34) NO.	(%)	Group 2 No. (34) NO.	(%)	t-test	P
Fever	6	14.7	3	8.8	3.29	0.07
Shivering	10	29.4	5	14.7	5.86	**0.015***
Vomiting	8	23.5	7	20.5	0.18	0.67
Headache	3	8.8	4	11.7	0.28	0.59
Dizziness	2	5.8	3	8.8	0.36	0.55
Diarrhea	5	14.7	4	11.7	0.28	0.59

Group 1 represents preoperative misoprostol group and group 2 represent postoperative misoprostol group. *Statistically significant difference ($P \leq 0.05$).

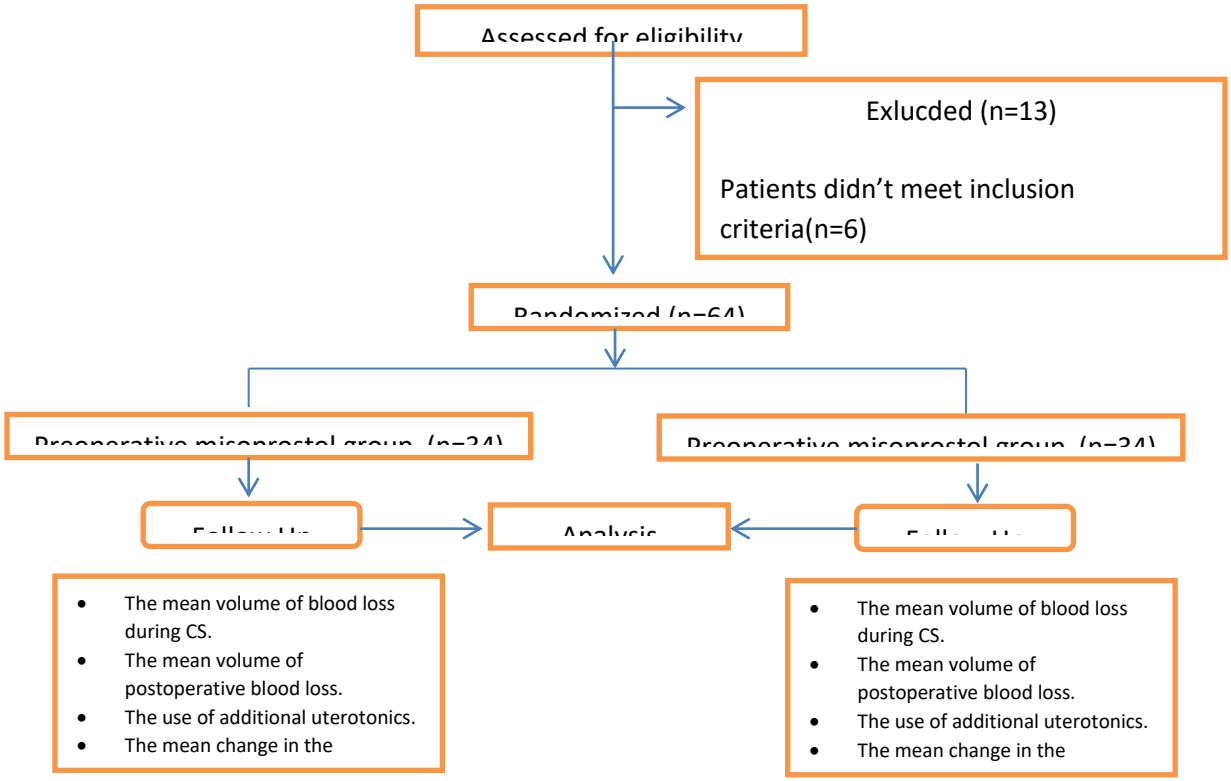

Figure 1: The study flowchart.

DISCUSSION

As regarding demographic data, there are non-significant differences between the groups under research in terms of maternal age, gravidity, parity, maternal BMI, and gestational age. That was in line with the results of another study. They demonstrated that demographic data on age, parity, gestation, and other factors did not differ significantly.

In the present investigation, no statistically significant difference between the two groups was found in the indications of cesarean section across the two groups. That was consistent with the Youssef et al. study [17]. In reference to blood loss in the current investigation, the two groups under study showed a statistically significant difference in blood loss, either intraoperatively or postoperative and overall blood loss on postoperative sublingual group than preoperative one.

The preoperative hemoglobin level was used to estimate blood loss, and the postoperative hemoglobin level was tested 24 hours later. The hematocrit level was measured in the recovery room one hour after surgery and soon after hospital admission in order to do a mathematical computation that estimated the amount of blood lost during the procedure. The following formula was used to determine the blood loss: Actual Blood Loss = [Hct1-Hct2 X Blood Volume].

Where: Blood volume = Body weight X 70 ml/Kg.

Hct 1 is the initial pre-operative hematocrit.

Hct 2 is the 1-hour post-operative hematocrit.

The statistical comparison between the two groups in our study revealed substantial differences in blood loss; the P value is ($P \leq 0.001$). Group 2 saw an intraoperative blood loss of 426.5±6.2 ml, compared to 395.1±4.1 ml in group 1, and a 24-hour postoperative blood loss of 85.4±8.6 ml, compared to 62.3±91 ml in group 1. Five studies that compared the use of oxytocin alone against misoprostol and oxytocin to minimize blood loss during cesarean birth excluded women who had all or some of the risk factors for PPH. The studies also varied with regard to the timing of misoprostol administration and the dosages of the conventional oxytocic drug and misoprostol.

Sublingual misoprostol was found to be equally effective as intravenous oxytocin (20IU) in preventing postpartum hemorrhage after cesarean delivery, with fewer adverse effects, when paired with a 20IU oxytocin drip (200μg) [17]. The degree to which blood loss was decreased, however, differed greatly throughout the investigations.

Compared to the group that included both high- and low-risk women, the researchers who excluded high-risk women found a higher reduction in intraoperative blood loss. Additionally, misoprostol was given preoperatively (rectally during catheterization or sublingually after intubation) in two of the studies that shown a higher reduction in blood loss. Reduced blood loss might have resulted from misoprostol being administered earlier [17].

In reference to the current study's pre and postoperative hemoglobin and HCT readings, the two groups under study showed a statistically significant difference ($P < 0.05$) in hemoglobin and HCT after surgery, with the preoperative sublingual group having a greater level than the postoperative one.

However, there was no statistically significant difference between the preoperative hemoglobin and HCT levels before and after treatment. According to Youssef et al. [17], group 1 had significantly higher postoperative hemoglobin and hematocrit levels ($p = 0.04$ and 0.007, respectively).

Compared to the preoperative group, more women in the postoperative sublingual group required extra oxytocin and ergometrine. But there was no statistically significant difference. In terms of medication side effects throughout our investigation, the preoperative sublingual group experienced more pyrexia and shivering than the postoperative sublingual group (47% versus 23.5%).

Within a few hours, every unpleasant incident went away on its own without any more issues. because high dosages (≥600 μg) of oral misoprostol are known to produce fever and shaking. The modest dosage (400 μg) and sublingual delivery method are responsible for the low incidence of side effects seen in this study.

Notably, life-threatening fevers above 40°C have been linked to extremely high dosages of misoprostol (1000 μg) [18]. Additionally, the systematic review found that women taking misoprostol were more likely to experience pyrexia and shivering. Hofmeyr asserted that the occurrence of misoprostol adverse effects was dose-dependent and that attempts should be made to determine the lowest safe and effective dosage of the medication [18].

There were no serious issues or statistically significant differences between the two groups in the current investigation regarding intraoperative

complications. Such is maternal mortality, PPH surgery, and the need for blood transfusions in either group. For almost ten years, misoprostol has been used to prevent and treat PPH. Numerous studies have been conducted globally to evaluate the efficacy of various misoprostol delivery routes for PPH prevention and control. However, opinions on the ideal dosage and the most effective method of administration are divided.

Hofmeyr et al. A meta-analysis found no additional benefit for greater doses of misoprostol in preventing bleeding over 1,000 cc [18]. Misoprostol 400 µg rectally administered prior to surgery was found to be more effective than postoperative administration in reducing blood loss during elective cesarean sections.

Additionally, the timing of misoprostol administration had no effect on the occurrence of adverse events. It's still difficult to determine when to administer anything to get the most efficiency. The current study's findings show that preoperative misoprostol administration considerably reduced blood loss. After the urine catheter is inserted and spinal anesthetic is administered. When misoprostol is taken orally, its absorption rate has been observed to be quicker. Having a half-life of 20 to 30 minutes and reaching a peak concentration after 12 minutes.

The effects of the rectal and vaginal routes are longer-lasting due to their slower absorption rates and lower peak concentrations after 60 minutes. Moreover, Compared to the sublingual route, slower absorption results in lower concentration levels and, as a result, fewer side effects [19]. Therefore, it is anticipated that the highest rate of issues will occur when the medication is taken orally. Consequently, in the current investigation. At the conclusion of the surgical procedure, the drug's bioavailability and concentration were probably at their highest. Therefore, it results in less blood loss and powerful uterine contractions.

Prior research with misoprostol has similarly demonstrated that preoperative administration of the medication reduces blood loss more effectively than postoperative treatment; nonetheless, the incidence of suspected medication side effects and problems was higher in these investigations.

CONCLUSIONS

Preoperative administration of sublingual misoprostol (400 µg) during CS is preferred over postoperative administration since it is associated with less hemoglobin level decline and less intraoperative and postoperative blood loss, even if fever and chills could still occur**.**

Limitations

Our study's possible flaw was that both study groups received oxytocin after the fetus was delivered, which might have affected the intraoperative blood loss. Also, PPH-free patients were included in the study. Lastly, we lacked a placebo group to evaluate the effectiveness of misoprostol usage.

Ethics declarations

The study received approval from the medical faculty's Institutional Ethics. University of Zagazig (ZU-IRB# 9050-17-11-2021), Following an explanation of the specifics, advantages, and hazards, each participant provided written informed permission. The study follows the Helsinki Declaration (1975), which is the World Medical Association's guideline of ethics for research involving human subjects.

Conflict of interest: The authors declare that they have no competing interest.

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