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Original Research Article

Adjunctive sublingual misoprostol for secondary prevention of post-partum hemorrhage during cesarean delivery: double blind placebo randomized controlled trial

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ABSTRACT

Background: Cesarean delivery is the most frequently performed major operative procedure worldwide. Objective of present study was to evaluate randomized evidence regarding efficacy and safety of sublingual misoprostol for secondary prevention of post-partum hemorrhage during and after cesarean delivery in women receiving prophylactic oxytocin as primary preventive tools and bleed around 500ml by visual analogue estimation.

Methods: A prospective, randomized, double-blind, placebo-controlled trial was performed at an obstetrics and gynecology department Aswan university hospital, Egypt, between October 2015 and September 2017. Women were eligible if they were undergoing elective cesarean under spinal anesthesia and were bleed around 500ml by visual analogue estimation. All participants received 10 IU oxytocin after delivery of the newborn. Participants were randomly assigned (1:1) to receive 400 µg misoprostol or matched placebo sublingually using a computer-generated random number sequence. Participants and providers were masked to assignment. The primary outcomes were intraoperative and postoperative blood loss.

Results: There was high significant reduction in intraoperative blood loss in misoprostol group (711.0 ± 188.41) compared with placebo group (915.33 ± 293.72) ($P=0.0001$). The all estimated blood loss during CS and 24 hours postoperative was significant lower in misoprostol group (890.39 ± 194.49) than that in placebo group (1096.9 ± 300.05) ($p=0.0001$).

Conclusions: Misoprostol as an adjunct to oxytocin as secondary prevention of post partum hemorrhage seemed to be more effectively reduce blood loss than did placebo with oxytocin alone.

Keywords: Cesarean delivery, Post-partum hemorrhage, Sublingual misoprostol

INTRODUCTION

Cesarean delivery is the most frequently performed major operative procedure worldwide. Compared with women delivering vaginally, women undergoing cesarean have an increased risk of high blood loss and so are more likely to need a blood transfusion.¹ The global rise in the incidence of cesarean delivery in the past decade has possibly contributed to the increase rate of postpartum

hemorrhage (PPH) in high-income countries.² The risk of PPH is further increased in the presence of risk factors such as multiple pregnancy, polyhydramnios, grand multiparity, severe pre-eclampsia, peripartum hemorrhage, prolonged and obstructed labor, augmented labor, obesity, and anemia.³

Postpartum hemorrhage is usually defined as the loss of more than 500 mL of blood after vaginal delivery and

1000 mL of blood after caesarean delivery.³ A leading cause of death in the developing world, accounting for 27% of maternal deaths. In well-resourced countries it is the most significant cause of maternal morbidity.³ Approximately 36% of all the lower segment CS deliveries are complicated by primary PPH. So estimated blood loss more than “average” or 500 mL should alert the obstetrician to possible excessive bleeding.⁴

A reduction of operative blood loss at cesarean section has a great benefit to the patients in terms of decreased postoperative morbidity and a decrease in risks associated with blood transfusions.⁴

Oxytocin, the gold standard oxytocic agent, is widely used during cesarean delivery to prevent PPH, even though some studies have raised concerns about its efficacy and adverse effects.^{5,6} Misoprostol has been evaluated as an alternative to oxytocin during cesarean delivery, and has also been used in combination with oxytocin.⁷⁻¹⁷ Two meta-analyses concluded that misoprostol was as effective as oxytocin and that the combination of the misoprostol and oxytocin is better than is oxytocin alone for the prevention of PPH. However, women with known risk factors for PPH, who are expected to benefit from an additional oxytocic agent, were excluded from some of the studies.^{12-14,16,17} Thus, the existing evidence on the optimal uterotonic agent during cesarean for high-risk women is insufficient.

Universal prophylaxis (primary prevention) lowers mean postpartum blood loss, which reduces the incidence of postpartum hemorrhage (PPH). However, administration of prophylactic uterotonics during cesarean section does not eliminate the need for treatment for some women.¹⁸

Improving obstetric care for the management of PPH remains difficult, although greatly needed. Reports from confidential enquiries into maternal deaths show that most deaths due to PPH involve delayed and substandard care in the diagnosis and management of hemorrhage.¹⁹

Misoprostol has a role in the management of uterine atony. Because of its wide variety of clinical applications, misoprostol is an active topic of research. Questions remain about the optimal dose and route, and whether prophylactic use should be limited to situations in which active management of the third stage of labor (oxytocin) is not possible. But its ease of administration, modest side-effect profile, lack of contraindications, and proven efficacy make it a useful option.²⁰

WHO maintained that there was still uncertainty about the lowest effective dose and optimal administration route of misoprostol for prevention of post-partum haemorrhage.²¹ However, adequate evidence is lacking to assess the effectiveness of misoprostol as adjunctive to oxytocin for preventing PPH, including the considerations about their doses and administration route and time. This study aims to examine randomized

evidence regarding comparative efficacy and safety of sublingual misoprostol for secondary prevention of post-partum hemorrhage during and after cesarean delivery in women receiving prophylactic oxytocin as primary preventive tools and bleed more than 500ml by visual analogue estimation.

METHODS

This study was a double blinded randomized controlled study conducted after local ethical committee agreement at Aswan University Hospitals from October 2015 to September 2017. Study inclusion Criteria were women who undergone elective cesarean section (C.S) and exposed to intraoperative bleeding about 500 ml diagnosed by visual analogue estimation due to atonic uterus. (Twin -grand multipara – macrosomia –breech–repeated previous caesarian delivery) were the indication of CS in our study. Women with medical disorder, placenta previa, placenta accrete, allergy to misoprostol and intraoperative bleeding due to causes other than uterine atony were excluded from the study.

Eligible participants

There were 980 pregnant women at term (37:40 weeks) gestation scheduled for elective low segment cesarean delivery under spinal anesthesia were invited for this study. 220 not meeting inclusion criteria and fifty refused to participate. 710 women undergone elective cesarean section, 530 women were excluded as they did not reach to 500 ml intraoperative bleeding and 180 women who reach about 500 ml intraoperative bleeding were included and continued the study. All participants undergone detailed history, general, abdominal and ultrasound examination. The participants who fulfilled the eligibility criteria were explained about the study with the beneficial and possible adverse effects of misoprostol. Informed consent was obtained from them.

Randomization

Patients were randomized into two groups, each compromised of ninety patients according to a two-blocked randomization list which was coded (1 or 2) at 1:1 ratio. The two parallel groups were prepared using a Computer-generated randomization system. The allocated groups will be concealed in serially numbered sealed opaque envelopes that will only be opened after recruitment. Patient allocation will be performed during CS by an independent person, who will not otherwise be involved in this study. The trial will be appropriately blinded; the participants, outcome assessors and the surgeon performing the procedure will be blinded to the medication type, which will be used.

Intervention

All women preformed CS by using spinal anesthesia, pfannenstiell incision of the skin, open of abdomen in

layers, lower uterine segment transverse incision. After delivery of the baby 10IU of oxytocin intravenous infusion administered by the anesthesiologist then delivery of the and placenta, during CS, intraoperative bleeding was estimated, if bleeding around 500 ml and due to atonic uterus then 400 µg of sublingual misoprostol (misotac) or placebo in form of ranitidine (ranitak) were administered. After that the blood loss was calculated to the end of the operation and 24 hours postoperative.

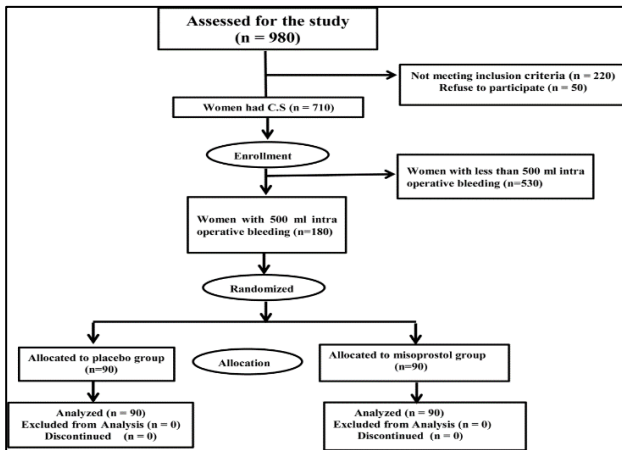


Figure 1: Flowchart of the study.

Blood loss estimation

Intraoperative blood loss was measured by adding the volume of the contents of the suction bottle which was changed after delivery of placenta to avoid being mixed with amniotic fluid and blood from parities and the difference in weight (in grams) between the dry and the soaked operation sheets and towels (1 gram = 1 ml.). Post-operative blood loss was measured by calculate the difference in weight (in grams) between the dry and the

soaked pads (1 gram = 1 ml). After that the total blood loss was calculated by the addition of intraoperative and postoperative blood loss.

Study outcome

The primary outcome was estimation of intraoperative, postoperative and total blood loss (ml).

The secondary outcome measures included need for blood transfusion, other surgical interventions, additional uterotonics and operative time. Also, Hemoglobin concentration was done in all patients preoperative and 24 hours postoperative and the change in concentration was noted. Any side effects such as fever, shivering, unpleasant taste, nausea, vomiting and diarrhea were recorded.

Statistical analysis

Data were entered and statistically analyzed using the Statistical Package for Social Sciences (SPSS) version 16. Qualitative data were described as numbers and percentages. Chi-square test was used for comparison between groups. Quantitative data were described as means (SD) or medians, as appropriate. They were tested for normality by Kolmogorov-Smirnov test. In the normally distributed variables, independent sample t-test was used for comparison between groups. In the non-normally distributed variables, Mann-Whitney test was used for comparison between groups. Odds ratios and their 95% confidence interval were calculated. "p value ≤ 0.05 " was considered to be statistically significant.

RESULTS

Out of 980 eligible women delivered by CS. 180 women were consented to participate and continued the study. They were randomized to two groups; misoprostol group and placebo group.

Table 1: Demographic criteria of the study groups.

Characteristics	Placebo group (n = 90)	Misoprostol group (n=90)	Significance
Age (year)	29.39±2.48	29.48±2.71	0.819
Weight (Kg)	78.32±6.16	78.33±6.16	0.990
Gestational age (week)	38.31±0.87	38.31±0.84	1.00
Parity	3 (1-8)	3 (1-9)	0.901
No. of CS	2 (0-5)	2 (0-5)	0.807
Indication of CS			
Twin	10 (11.1)	11 (12.2)	
Breech	15 (16.7)	14 (15.6)	0.967
Macrosomia	15 (16.7)	13 (14.4)	
Repeated CS	50 (55.6)	52 (57.8)	
Initial Hemoglobin	10.62±0.73	10.63±0.77	0.961

C.S (cesarean section). #Variables are presented as mean±standard deviation, median (minimum-maximum) and number (percentage).

There was no significant difference between the two groups with respect to their age, weight, gestational age, parity, number of CS, indication of CS and initial hemoglobin (Table 1). There was high significant reduction in intraoperative blood loss in misoprostol group (711.0 ± 188.41) compared with placebo group (915.33 ± 293.72) ($P=0.0001$). However, there was no

significant difference in post-operative bleeding between the two groups. ($p=0.831$).

The all estimated blood loss during CS and 24 hours postoperative was significant lower in misoprostol group (890.39 ± 194.49) than that in placebo group (1096.9 ± 300.05) ($p=0.0001$) (Table 2).

Table 2: Primary outcome of the study groups.

Variables	Placebo group (n = 90)	Misoprostol group (n = 90)	Significance
Intra-operative blood loss (ml)	915.33±293.72	711.0±188.41	0.0001*
Post-operative blood loss (ml)	181.56±34.26	180.5±31.98	0.831
All blood loss(ml)	1096.9±300.05	890.39±194.49	0.0001*

*Statistically significant, #Variables are presented as mean±standard deviation

The incidence of blood transfusion was increased in placebo group 50 (55.6%) women compared with 18 (20.0%) women in misoprostol group, ($P=0.0001$). More women in placebo group (66.7%) than in misoprostol group (26.7%) required additional uterotonics ($p=0.0001$). Also, more women in placebo group (36.7%) than in misoprostol group (10.0%) required more

surgical intervention ($p=0.0001$). There was a highly significant reduction in operative time in misoprostol group (70.29 ± 15.52) compared with placebo group (98.1 ± 9.85) ($P= 0.0001$). There was no significant difference in related to 24-hour post-operative hemoglobin concentration between the two groups. ($p=0.245$) (Table 3).

Table 3: Secondary outcome of the study groups.

Variables	Placebo group (n=90)	Misoprostol Group (n = 90)	Significance
Blood transfusion	50 (55.6)	18 (20.0)	0.0001*
Additional Uterotonics	60 (66.7)	24 (26.7)	0.0001*
Extra surgical intervention	33 (36.7)	9 (10.0)	0.0001*
Operative time	98.1±9.85	70.29±15.52	0.0001*
Post-operative hemoglobin	9.72±0.66	9.84±0.73	0.245

*Statistically significant, #Variables are presented as number (percentage) and mean±standard deviation.

Table 4: Side effect of the study groups.

Side effect	Placebo group (n=90)	Misoprostol Group (n=90)	Significance
Fever	11 (12.2)	37 (41.1)	0.0001*
Shivering	13 (14.4)	34 (37.8)	0.0001*
Nausea	13 (14.4)	15 (16.7)	0.681
Vomiting	7 (7.8)	9 (10.0)	0.600
Diarrhea	3 (3.3)	8 (8.9)	0.120
Unpleasant taste	2 (2.2)	13 (14.4)	0.003*

*Statistically significant, #Variables are presented as number (percentage).

About the side effect, there was significant increase in incidence of fever (41.1%), shivering (37.8%) and unpleasant taste (14.4%) in misoprostol group than placebo group [fever (12.2%), shivering (14.4%) and unpleasant taste (2.25)] ($p=0.0001$, 0.0001 and 0.003 respectively) however there was no significant difference between the two groups in related to nausea, vomiting

and diarrhea ($P= 0.681, 0.600$ and 0.120 respectively) (Table 4).

Study power calculation

As the average amount of blood loss was the primary outcome of this research, study power was calculated online (www.dssresearch.com) using the average value of

the placebo group (1096.9 ± 300.05) and that of the misoprostol group (890.4 ± 194.9), the sample size was 90 for each group with 95% confidence level. The study power was found to be 100%.

DISCUSSION

The long life outside the refrigerator and oral administration of misoprostol make it attractive for use in in prevention and management of post-partum hemorrhage especially low-resource areas. It also has no effect on blood pressure or cause Broncho-constriction, and so can be safely used in women with asthma.²¹ As regard the use of misoprostol for PPH prophylaxis, it appears that it reduces postpartum blood loss, but that it is not as effective as oxytocin. Oxytocin is therefore now recommended over misoprostol as a first line for PPH prophylaxis.²¹ Instead of sudden massive hemorrhage, postpartum bleeding is frequently steady. So that estimated blood loss is commonly only approximately half the actual loss. If atony persists, bleeding may appear to be only moderate at any given instant but may continue until serious hypovolemia develops.²¹

In present study we hypothesized that the adjunctive use of misoprostol for secondary prevention of post-partum hemorrhage may be beneficial after administration of oxytocin as primary preventive tool for prevention of post-partum hemorrhage during cesarean section when estimated blood loss more than "average" or 500 mL.

At the best of our knowledge we are the first to address this issue with the main outcome of our results were that adjunctive use of sublingual misoprostol decreases number of cases with postpartum hemorrhage with decrease the main intraoperative and total blood loss during cesarean section where there was increase blood loss around 500ml by visual estimation of blood loss during cesarean section. There was high significant reduction in intraoperative blood loss in misoprostol group (711.0 ± 188.41) compared with placebo group (915.33 ± 293.72) ($P=0.0001$). The all estimated blood loss during CS and 24 hours postoperative was significant lower in misoprostol group (890.39 ± 194.49) than that in placebo group (1096.9 ± 300.05) ($p=0.0001$).

Widmer et al recruited 1400 women with PPH and compared the use of combined oxytocin and misoprostol (600 µg) with the use of oxytocin alone.²² The results show no difference between groups in additional loss of 500 ml (risk ratio, RR 1.01; 95% confidence interval, 95% CI 0.78-1.30) or 1000 ml (RR 0.76; 95% CI 0.43-1.34). The conclusion is that in settings where oxytocin is available for the treatment of PPH, there is no role for additional misoprostol.²²

Two studies compared the efficacy of misoprostol and oxytocin as first-line treatments for PPH. The studies recruited a total of 40 000 women from a range of units throughout the world, some of which routinely gave

oxytocin for prophylaxis, and some that gave no prophylaxis.^{23,24} The women who developed PPH were randomized to receive a high-dose oxytocin infusion (40 iu over 15 minutes) or misoprostol (800 µg, sublingually), each with placebos so as to ensure double blinding. In the units where there was no oxytocin prophylaxis there was less additional blood loss in those given oxytocins than for those given misoprostol. The difference was statistically significant for an extra loss of 300 ml (RR 1.78; 95% CI 1.40-2.26), but not for a loss of over 1000 ml (RR 1.67; 95% CI 0.40-6.96). In the units where women were given routine oxytocin prophylaxis, there was no difference in additional blood loss of 300 ml (RR 1.12; 95% CI 0.92-1.37), but more women in the misoprostol group had an additional loss of over 1000 ml (RR 3.61; 95% CI 1.02-12.85).

Compared with other routes of administration, sublingual and oral misoprostol have the shortest time to reach peak concentration (26-28 minutes, with a median time of 20 minutes), which is approximately one-third of the time of the vaginal route. Sublingual misoprostol also has the highest peak concentration and greatest bioavailability: 400 µg administered sublingually approaches nearly twice the peak concentration of oral administration, and reaches between three and four times the concentration measured after vaginal administration.²⁵ The avoidance of first-pass metabolism via the liver achieves a higher peak concentration by sublingual administration than by oral administration. This characteristic makes sublingual misoprostol more suitable than other routes of administration for clinical applications requiring a rapid onset of action, such as that required for the prevention of PPH.²⁵

Two systematic reviews, which includes the 2014 Cochrane review, focused on misoprostol to treat PPH and examined the optimal route and dosage, and its efficacy.^{20,26} Compared with 40 IU oxytocin infusion, 800 micrograms sublingual misoprostol was associated with a significant increase in the number of women who had blood loss of at least 1000 ml (RR 2.65, 95% CI 1.04-6.75) and who required blood transfusion (RR 1.47, 95% CI 1.02-2.14). The authors concluded that oxytocin infusion should be recommended as first-line treatment for primary PPH. When used following prophylactic uterotonics, misoprostol and oxytocin infusion work similarly.

Lokugamage AU et al, conduct randomized single blinded two-center study, in South Africa. Sixty-four women with primary post-partum hemorrhage due to an atonic uterus were recruited. The primary outcome measure was whether the hemorrhage ceased within 20 minutes of administering the first line treatment, once hemorrhage was clinically recognized. There was a 28.1% difference between the misoprostol arm and the Syntometrine and Syntocinon arm ($p=0.01$). The authors concluded that misoprostol appears to be better than

Syntometrine with a Syntocinon infusion at treating postpartum hemorrhage when caused by uterine atony.²⁷

Othman ER et al conducted a randomized clinical trial on 120 pregnant women at term (37-40 weeks) gestation scheduled for elective cesarean delivery, who were assigned to either sublingual misoprostol 400 µg or intravenous infusion of 20 units of oxytocin after delivery of the neonate. The overall mean blood loss was significantly lower in the misoprostol group compared to the oxytocin group (490.75±159.90 mL vs. 601.08±299.49 mL; p=0.025). However, changes in hematocrit level (pre- and postpartum) was comparable between both groups. There was a need for additional oxytocic therapy in 16.7% and 23.3% after use of misoprostol and oxytocin, respectively (p = 0.361). Incidence of side effects such as shivering and metallic taste were significantly higher in the misoprostol group compared to the oxytocin group (p < 0.001).²⁸

Two studies have combined misoprostol and oxytocin for the prevention of PPH at CS.^{30,31} The first one studied the effect of adding 200 µg of sublingual misoprostol after delivery of the fetus to 20 IU of oxytocin given routinely to all cases and reported that the addition of misoprostol was effective in reducing blood loss.²⁹ The second study enrolled a small sample (n = 56) of women undergoing emergency CS who received 5 IU of intravenous oxytocin after cord clamping and were randomized to further receive either misoprostol orally or oxytocin infusion intravenously, no difference in blood loss was noticed between the two groups, although there was no control group included to assess whether either intervention had any added value.³⁰

Singh showed that sublingual misoprostol at doses of both 400 and 600 µg was more effective compared to either 5 IU of intravenous oxytocin or 200 µg of intravenous methylergometrine in decreasing blood loss during the third and fourth stages of labor.³¹

Chaudhuri et al conduct a randomized controlled study demonstrated that 400 µg of sublingual misoprostol was a safe and effective therapeutic alternative to 10 IU of intramuscular oxytocin in the routine management of third stage labor for prevention of PPH among low-risk women.³²

In present study as regard the side effect, there was significant increase in incidence of fever (41.1%), shivering (37.8%) and unpleasant taste (14.4%) in misoprostol group than placebo group [fever (12.2%), shivering (14.4%) and unpleasant taste (2.25).] (p=0.0001, 0.0001 and 0.003 respectively), this results in agreement with results from the different study.^{7-9,14,22,28}

One limitation of present study was we did not use alkaline hematin method which is a validated method for accurate measurement of blood loss, but we used in state

a gravimetric method to measure the amount of blood loss.³³

Marcel H et al in veterinary surgery compare gravimetric and colorimetric methods of quantifying surgical blood loss and conclude that Estimation of blood loss using a gravimetric method is accurate and objective tool to evaluate intraoperative blood loss.³⁴

One of the strength of present study was that double blind randomized study provides the evidence that Misoprostol as an adjunct to oxytocin as secondary prevention of postpartum hemorrhage may seemed to more effectively reduce blood loss than did placebo with oxytocin alone. Another strength of our study as the average amount of blood loss was the primary outcome of this research, study power was calculated online was found to be 100%.

CONCLUSION

A single dose of 400 µg sublingual misoprostol as an adjunct to oxytocin as secondary prevention of postpartum hemorrhage may be more effectively reduce blood loss than did placebo with oxytocin alone. Investigation of misoprostol use in larger population groups and with different dosages and another route together with comparison of other methods used to reduce bleeding cesarean section, is required.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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