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Original Article

Sublingual misoprostol versus intravenous oxytocin in reducing bleeding during and after cesarean delivery: A randomized clinical trial

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ABSTRACT

Objective: This study compares the efficacy of sublingual misoprostol versus intravenous oxytocin in reducing bleeding during and after cesarean delivery.

Materials and methods: A randomized clinical trial conducted 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 main outcome measures were blood loss at and 2 hours after cesarean delivery, change in hematocrit value, need for any additional oxytocic drugs, and drug-related side effects.

Results: 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 ($p < 0.001$).

Conclusions: Sublingual misoprostol is more effective than intravenous infusion of oxytocin in reducing blood loss during and after cesarean delivery. However, occurrence of temporary side effects such as shivering and metallic taste was more frequent with the use of misoprostol.

Introduction

According to the World Health Organization, postpartum hemorrhage (PPH) continues to be the most significant cause of maternal morbidity and mortality worldwide [1]. Average blood loss during delivery is progressively more with the type of delivery, vaginal delivery (500 mL of blood), cesarean delivery (1000 mL), and emergency hysterectomy (3500 mL) [2].

A reduction of blood loss during cesarean delivery has a great benefit to decrease postoperative morbidity and decrease the risks associated with blood transfusions [3]. The routine use of oxytocin is associated with a significant reduction in the occurrence of PPH [4].

Although many hospitals use oxytocin as the first line to prevent uterine inertia during cesarean delivery, it may not be the ideal agent for prevention of PPH especially in compromised patients with preeclampsia, cardiac disease or prolonged labor [5]. Oxytocin increases the heart rate and has negative inotropic, antiplatelet, and antidiuretic effects [6].

Excessive blood loss is estimated by a 10% drop in the hematocrit value postdelivery or by need for blood transfusion. This occurs in approximately 4% of vaginal deliveries and 6% of cesarean deliveries [7].

Misoprostol, a PGE1 analogue, has been shown in many studies to be an effective myometrial stimulant of the pregnant uterus and selectively binds to EP-2/EP-3 prostanoid receptors [8]. Misoprostol administration, either by oral or rectal route, has been shown to be effective in preventing PPH or is considered as an effective

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alternative to other conventional oxytocic drugs especially in developing countries as it is cheap and thermostable [9]. Pharmacokinetic studies suggest that the bioavailability of misoprostol after sublingual administration is higher than after oral or vaginal administration [10].

Many management protocols for prevention of PPH have been reported and continuously improved to reduce anxiety to the patients [11]. Misoprostol, a PGE1 analogue, has been used both for prevention and management of PPH due to its strong effect on the uterus; however, there is no consensus on optimal dose or route of administration [12]. In the majority of these studies, misoprostol has been administered either orally or rectally in dosages ranging from 400 μg to 1000 μg [13].

A few studies are now available for the use of sublingual misoprostol in the prevention of blood loss following vaginal delivery and have reported its effectiveness and convenient route of administration [14].

The current study compares the efficacy of sublingual misoprostol to intravenous oxytocin in the prevention of blood loss following cesarean delivery. As recommended by Cochrane reviews, there is an urgent need for well-designed randomized trials to assess the risks and benefits of misoprostol [15].

Material and methods

The current study is a clinically registered open, parallel, randomized clinical trial (NCT02562300) comparing the effect of sublingual misoprostol to intravenous oxytocin in the prevention of blood loss following cesarean delivery. The ethical review board of the Faculty of Medicine of the Assiut University approved the study. The participants were recruited from the Outpatient Obstetrics Clinic of the Assiut Women's Health Hospital. It was carried out in the period between January 1, 2015 and April 1, 2015. This trial was designed and reported according to the revised recommendations of ClinicalTrials.gov for improving the quality of reporting randomized clinical trials.

Eligible participants

There were 120 pregnant women at term (37–40 weeks) gestation scheduled for elective low segment cesarean delivery under spinal anesthesia enrolled in this study (Figure 1).

Women with anemia (hemoglobin < 8 g), multiple gestation, placental abnormality (e.g. placenta previa, placenta abruption), polyhydramnious, two or more previous cesarean deliveries, current or previous history of heart disease, liver, renal disorders or known coagulopathy were excluded from the study.

Randomization

Randomization was done using a computer-generated random table. Eligible patients who consented were randomly assigned to receive either sublingual misoprostol or intravenous oxytocin after delivery of the fetus. Allocation concealment was done using serially numbered closed opaque envelopes. Each envelope was labeled with a serial number and had a card noting the intervention type inside. Allocation was never changed after opening the envelopes.

Intervention

Eligible participants were allocated to one of two groups. The sublingual misoprostol group received 400 μg of sublingual misoprostol, immediately after delivery of the neonate. The oxytocin group received 20 IU oxytocin dissolved in 1 L of lactated Ringer's or saline solution and infused at the rate of 125 mL/h, immediately after delivery of the neonate. Additional oxytocic therapy was given if the uterine tone was inadequate. The volume of blood loss during cesarean delivery and 2 hours postoperatively was assessed. Total blood loss during cesarean delivery was measured by adding the volume of the suction bottle with the blood soaked sponges (know dry weight). Blood loss 2 hours after cesarean delivery was measured by using blood collection drape. The whole blood loss was estimated by adding the blood in the suction bottle, blood soaked sponges and blood collection drape.

Hematocrit values were determined before surgery and 24 hours following surgery. Vital signs were observed continuously intraoperative and every 30 minutes after that.

Study outcomes

The primary outcome of this study was estimation of blood loss during and after cesarean delivery following administration of sublingual misoprostol or intravenous oxytocin.

The secondary outcome measures included the need for any additional oxytocic drugs, changes in hematocrit value after delivery, and incidence of side effects.

Sample size

Sample size was calculated based on the primary outcome (blood loss in women after cesarean delivery), taking mean blood loss with the use of oxytocin as 974 mL with a standard deviation of 285 mL [16]. Assuming that sublingual misoprostol is more effective than oxytocin in reducing blood loss by 155 mL, 60 participants in each group will have > 80% power at 5% significance to detect such a difference (Epi-info: Centers for Disease Control and Prevention, Atlanta, GA, USA).

Statistical analysis

The data were collected and entered into a Microsoft Access database and analyzed using SPSS version 21 (SPSS Inc., Chicago, IL, USA). The demographic and baseline data were compared between the groups. The outcome variables were calculated using a paired t test to compare continuous variables before and after treatment and using an unpaired t test between groups. For dichotomous variables, Chi-square was used to estimate the significance value. For analysis, $p < 0.05$ was considered significant.

Results

This study included 120 women. All recruited women had an elective cesarean delivery. None of the patients required conversion to general anesthesia during the surgery. The demographic data of the two groups are shown in Table 1. There were no significant statistical differences between both groups with regard to the demographic data.

The misoprostol group reported a larger reduction in intraoperative blood loss compared with the oxytocin group (160.75 ± 85 mL, 376.08 ± 75 mL, $p = 0.025$). Although the misoprostol group also reported a higher reduction in blood loss postoperatively in comparison with the oxytocin group, this difference did not reach statistical significance ($p = 0.067$).

Finally, the overall estimated mean blood loss was significantly lower in the misoprostol group (490.75 ± 159.90 mL) compared to the oxytocin group (601.08 ± 299.49 mL, $p = 0.025$; Table 2).

There was no statistical significant difference between both groups as regard to pre- and postpartum hematocrit values ($p = 0.453$ and 0.432, respectively). The mean reduction of hematocrit was 3.61% in the misoprostol group and 3.63% in oxytocin

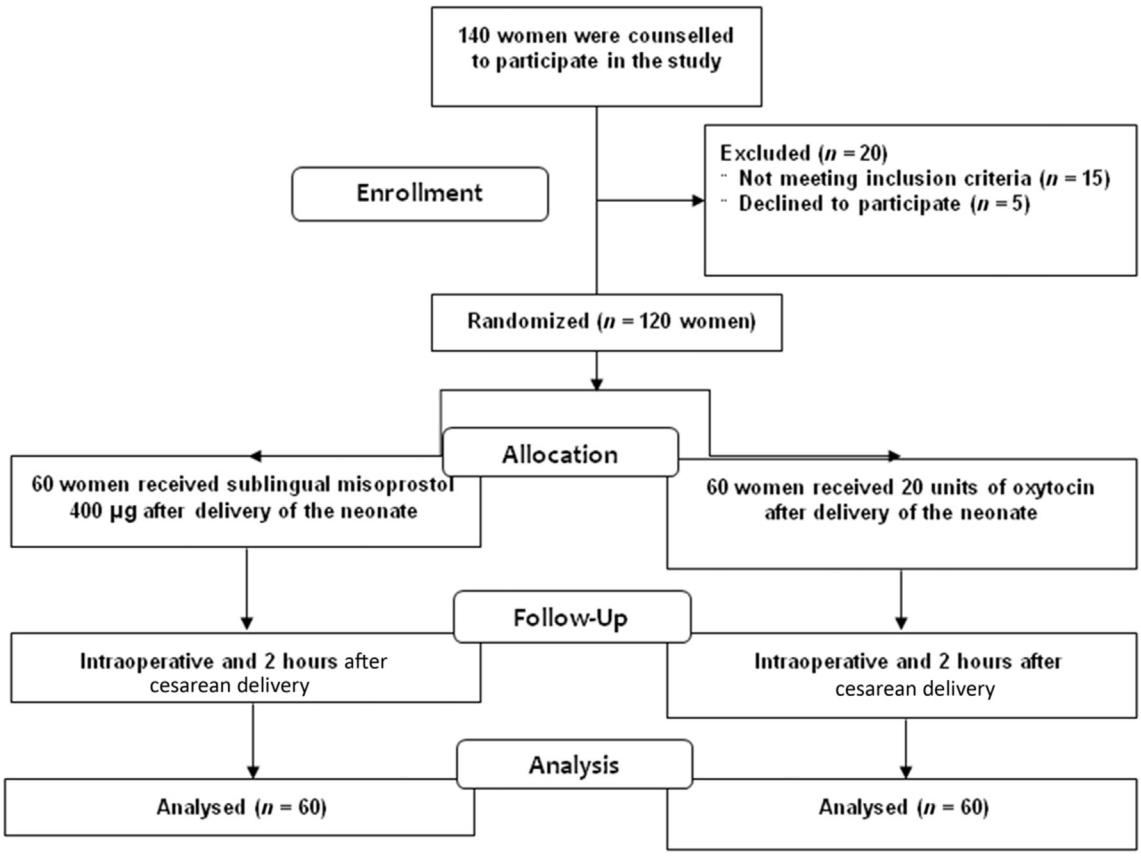

Figure 1. The study flowchart.

group. Both treatment groups were comparable with regard to duration of the cesarean delivery without significant difference between both groups ($p = 0.620$). The need for additional oxytocic drugs was more frequent in the oxytocin group (14 women) than in the misoprostol group (10 women); however, this difference did not reach statistical significance ($p = 0.361$; Table 3).

The observed maternal side effects are summarized in Table 4. No statistically significant difference between both groups was reported as regard to pyrexia (1 case in the misoprostol group vs, 4 cases in oxytocin group). However, shivering and metallic taste were reported in the misoprostol group more than in the oxytocin

Table 1
Baseline characteristics of the recruited women in the study.

Characteristic	Sublingual misoprostol ($n = 60$)	Oxytocin ($n = 50$)	p
Age (y)	25.38 ± 5.48	23.87 ± 4.41	0.137
Maternal weight (kg)	79.90 ± 7.66	77.47 ± 7.97	0.146
Number of abortions	0.44 ± 0.81	0.58 ± 1.18	0.761
Number of normal delivery	1.20 ± 1.42	1.18 ± 1.72	0.350
Number of previous CDs (once)	24	20	0.449
Gestation age (wk)	38.95 ± 1.16	38.53 ± 1.16	0.051
Birth weight (g)	3330.3 ± 397.8	3306.7 ± 624.3	0.249

Data are mean ± standard deviation or *n*.
CD = cesarean delivery.

Table 2
The blood loss during and after cesarean delivery (the primary outcome).

Characteristic	Sublingual misoprostol ($n = 60$)	Oxytocin ($n = 50$)	p
Blood loss (mL)			
Intraoperative	160.75 ± 85	376.08 ± 75	0.03*
2-h postoperative	330 ± 88	225 ± 80	0.067
Overall blood loss	490.75 ± 159.90	601.08 ± 299.49	0.025*

Data are mean ± standard deviation or *n*. * Statistically significant difference ($p < 0.05$).

Table 3
The secondary outcome measures.

Characteristic	Sublingual misoprostol ($n = 60$)	Oxytocin ($n = 50$)	p
Hematocrit (%)			
Preoperative	36.69 ± 3.34	37.12 ± 3.22	0.453
Postoperative	33.08 ± 3.26	33.49 ± 3.20	0.432
Duration of surgery (min)	37.88 ± 8.13	36.50 ± 7.55	0.620
Use of additional oxytocic drug	10	14	0.361

Table 4
The reported side effects of the drugs.

Characteristic	Sublingual misoprostol ($n = 60$)	Oxytocin ($n = 50$)	p
Pyrexia	1	4	0.361
Shivering	36	9	< 0.001
Vomiting	1	15	< 0.001
Headache	3	20	< 0.001
Metallic taste	21	0	< 0.001
Giddiness	0	19	< 0.001

Table 5
Summary of some randomized controlled trials of sublingual/oral misoprostol in management of postpartum blood loss.

Author	Year	Number of patients	Intervention	Effects
Walley et al [17]	2000	401	Oral Misoprostol 400 μg IM 1 mL oxytocin 10 IU	Oral misoprostol appears to be as effective in minimizing blood loss in the third stage of labor as IM oxytocin
Acharya et al [18]	2001	60	Oral Misoprostol 400 μg IV Syntocinon 10 IU	Oral misoprostol appears to be safe and as effective as IV syntocinon in reduction of intra-operative blood loss during elective cesarean delivery
Walraven et al [20]	2004	160	Misoprostol 600 μg (200 μg orally and 400 μg sublingually) versus placebo	Misoprostol was more effective than placebo in the treatment of PPH
Lam et al [8]	2004	60	Sublingual Misoprostol 600 μg IV 1 mL syntometrine	Sublingual misoprostol was effective as IV syntometrine in reducing amount of *postpartum* blood loss
Hoj et al [21]	2005	661	Sublingual Misoprostol 600 μg versus placebo	Sublingual misoprostol was effective in reduction of the frequency of severe PPH
Vimala et al [16]	2006	100	Sublingual Misoprostol 400 μg IV 20 units of oxytocin	Sublingual misoprostol appears to be as effective as IV infusion of oxytocin in reducing blood loss at cesarean delivery
Nielsen et al [22]	2006	—	Sublingual misoprostol 600 μg versus placebo	The sublingual misoprostol reduces the frequency of severe PPH
Gulmezoglu et al [23]	2007	9264	Oral Misoprostol 600 μg IV or IM oxytocin 10 IU	10 IU oxytocin (IV or IM) is preferable to 600 μg oral misoprostol in the active management of the third stage of labor
Baskett et al [19]	2007	622	Oral Misoprostol 400 IV Oxytocin 5 IU	Use of 400 μg of oral misoprostol was effective as 5 IU of IV oxytocin in reducing blood loss after delivery
Enakpene et al [24]	2007	864	Oral misoprostol IM Methylergometrine	Orally administered misoprostol was more effective in reducing blood loss during the third stage of labor than IM methylergometrine.

IM = intramuscular; IU = international unit; IV = intravenous; PPH = postpartum hemorrhage.

group (36 cases in the misoprostol group vs. 9 cases in oxytocin group and 21 cases in the misoprostol group vs. 0 in the oxytocin group, respectively; $p < 0.001$). Vomiting, headache, and giddiness were more commonly seen in the oxytocin group compared to the misoprostol group ($p < 0.001$).

Discussion

The present work demonstrates superiority of sublingual misoprostol (400 μg) to intravenous oxytocin (20 IU) regarding efficacy and safety. The misoprostol group showed a significant reduction in blood loss during cesarean delivery and 2 hours later when compared to oxytocin.

Some studies [8,21–23] have reported that the hemoglobin concentration tends to be less in the misoprostol group than other groups: we found in that present study that the hematocrit value was higher in the misoprostol group in comparison to the oxytocin group but without statistical significant difference.

Most reported studies used sublingual misoprostol to manage PPH; nevertheless, a few studies used it as a preventive measure, as we did. Our study supports the fact that sublingual misoprostol is more effective than oxytocin in reducing postpartum blood loss and that more patients in the oxytocin group required additional oxytocic drugs but without statistical significance. In comparison to the oral and rectal route, sublingual administration is more convenient, leads to rapid absorption, and effects are comparable.

Our study was also in accordance with findings from Vimala et al [16], Walley et al [17], Acharya et al [18], and Baskett et al [19] who found that oral/sublingual misoprostol 400 μg appears to be as effective in minimizing blood loss in the third stage of labor as oxytocin.

Walraven et al [20], Lam et al [8], Hoj et al [21], Nielsen et al [22], and Gulmezoglu et al [23] used oral/sublingual misoprostol 600 μg in the treatment of PPH and proved its effectiveness in decreasing the amount of postpartum blood loss. Table 5 shows a summary of randomized controlled trials studying sublingual/oral misoprostol in the management of postpartum blood loss.

The incidence of side effects such as shivering and metallic taste in women receiving misoprostol was significantly higher than that in the oxytocin group. These findings are similar with results of other studies [8,16–23].

Limitations of the present work include unfeasibility to blind study participants to avoid overdose of the used drug, the subjective and interobserver error in clinical judgment assessing uterine contraction, and the small sample size that was available for final analysis. Also, measures are needed to overcome the common side effects associated with sublingual misoprostol such as shivering and metallic taste.

Conclusion

Sublingual misoprostol appears to be a preventive alternative to intravenous oxytocin in reducing blood loss during and after

cesarean delivery without significant major side effects; in the future, it may be an important and effective option for management of third stage labor particularly in women where oxytocin is contraindicated.

Conflicts of interest

None of the authors have any conflict of interest.

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