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Effects of Preoperative Sublingual Misoprostol on Uterine Tone during Isoflurane Anesthesia for Cesarean Section

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Summary: El-Tahan MR, Warda OM, Rashad A, Yasseen AM, Ramzy EA, Ahmady MS, Diab DG, Matter MK – Effects of Preoperative Sublingual Misoprostol on Uterine Tone during Isoflurane Anesthesia for Cesarean Section.

Background and objectives: Misoprostol would reduce the uterine bleeding after cesarean delivery without harmful effects on either mother or baby. We aimed to evaluate the effects of preoperative misoprostol on maternal blood loss, uterine tone, and the need for additional oxytocin after cesarean delivery under isoflurane anesthesia.

Methods: After ethical approval, 366 patients scheduled for elective cesarean delivery were randomly allocated to receive either sublingual misoprostol 400 μg (n = 179) or placebo tablet (n = 187) after intubation. Anesthesia was maintained with 0.5-0.7 MAC isoflurane with nitrous oxide. All patients received intravenous infusion of 10 IU of oxytocin after placental delivery. Perioperative estimated blood loss, uterine tone, need for supplementary oxytocin, hematocrit, Apgar scores at 1 and 5 min and adverse effects were recorded.

Results: After induction, patients receiving sublingual misoprostol had significant less perioperative estimated blood loss (202 ± 383.1 vs. 708 ± 204.3 mL, $p < 0.001$), need for oxytocin ($p < 0.001$), higher hematocrit levels ($p < 0.001$) and uterine tone ($p < 0.02$). The incidence of shivering was higher in the misoprostol group ($p = 0.04$). There were no differences between the two groups as regarding Apgar scores, nausea and vomiting, gastrointestinal disturbances and pyrexia.

Conclusion: Preoperative administration of sublingual misoprostol 400 μg is safe and effective in attenuating the maternal bleeding and uterine atony from isoflurane anesthesia for cesarean delivery.

Keywords: Anesthesia, Obstetrical; Cesarean Section; Isoflurane; Hemorrhage; Misoprostol.

INTRODUCTION

Volatile anesthetics such as sevoflurane, desflurane, and isoflurane are commonly used for cesarean delivery. Isoflurane is widely used for cesarean delivery in many centers because of its low cost and blood-gas partitioning coefficient and rapid elimination from the foetus [1]. General anesthesia is commonly used for cesarean delivery at the authors' centre because of the refusal of parturient for regional anesthesia. A Cochrane review failed to show that regional anesthesia is superior to general anesthesia in terms of major maternal or neonatal outcomes [2].

Isoflurane, similar to other inhalational anesthetics, has been shown a dose-dependent, induced myometrial relaxation in 25% of parturient with added risks of postpartum hemorrhage with the use of minimum alveolar concentration (MAC) from 0.5 to 2.35 [3-5]. This may be mediated through the inhibition of the oxytocin-induced contraction [6], decrease in intracellular concentration of free calcium [7], inhibition of voltage-dependent calcium channels activity [8], and activation of adenosine triphosphate-sensitive potassium channels (K ATP) [9] of pregnant uterine smooth muscle.

Several uterotonics such as oxytocin reduce postpartum hemorrhage by inducing uterine contraction, but with added risks of hemodynamic adverse effects [10].

Sublingual or rectal misoprostol, a prostaglandin E1 analogue, in doses of 100 to 800 μg is as safe and effective as intravenous infusion of oxytocin in reducing blood loss and the need for additional oxytocin after cesarean delivery, under either spinal or general anesthesia, with occurrence of transient side effects such as nausea, shivering and pyrexia [11-17]. Misoprostol possess several advantages over oxytocin, including long shelf life, stability at room temperature, and possible buccal, rectal and sublingual administration [11,16]. The

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latter has many advantages such as rapid uptake, long-lasting duration of effect and greatest bioavailability, compared with other routes of misoprostol administration [18].

Up to our best knowledge, this trial was the first one to study the inhibitory effects of misoprostol on the uterine atony of inhalational anesthetics.

We postulated that the use of sublingual misoprostol during isoflurane anesthesia for routine cesarean delivery would reduce maternal hemorrhage, uterine atony, and the need for additional uterotonic agents, without harmful effects on either mother or baby. Therefore, the present study was designed to evaluate the effects of preoperative sublingual misoprostol on maternal blood loss, uterine tone, the need for additional oxytocin and neonatal outcome during isoflurane anesthesia for routine cesarean delivery.

METHODS

Three hundred eighty-two American Society of Anesthesiologists (ASA) class I and II parturients aged 18-35 years with uncomplicated singleton pregnancies of at least 36 weeks' gestation scheduled for elective cesarean delivery via a Pfannenstiel incision under general anesthesia were included in this randomized, double-blinded, placebo-controlled study after obtaining approval of the local ethical committee and an informed written consent from all participants who refused regional anesthetic techniques and requested general anesthesia. Indications for cesarean delivery included breech presentation, cephalopelvic disproportion or previous cesarean delivery. All operations were performed by the same surgeons. The protocol was registered with www.clinicaltrials.gov with the number of [NCT01466530].

Based upon previous study [19], the mean blood loss after oral administration of misoprostol during cesarean delivery was 970 ± 560 mL. *A priori* power analysis indicated that 174 patients in each group would be sufficient to detect a 20% reduction in blood loss after cesarean delivery, with a type-I error of 0.05 and a power of 90%. We added 10% more patients to account for patients dropping out during the study.

Women with a history of allergy to prostaglandins, bronchial asthma, anemia, bleeding disorders, cardiac, inflammatory bowel disease, with multiple pregnancies, preeclampsia, placenta previa, abruptio placenta, previous postpartum hemorrhage, antepartum hemorrhage, with the presence of conditions requiring prophylactic oxytocin infusion after delivery such as grand multiparity (parity ≥ 4), presence of uterine fibroids, evidence of intrauterine growth restriction or other fetal abnormality were excluded from the study.

Patients were randomly allocated to receive sublingual 400 μg of misoprostol or identical placebo two tablets after tracheal intubation before surgery.

Primary outcome included the estimated blood loss after cesarean delivery. Secondary outcome variables included the changes in uterine tone, pre- to post-delivery hematocrit levels, the need for additional oxytocin or blood transfusion, neonatal outcome and adverse effects after the use misoprostol during isofluarane anesthesia.

Anesthetic management was standardized in all studied patients. Oral ranitidine 150 mg was given the night before and on the morning of surgery and 0.3 mol.L^{-1} sodium citrate (30 mL) was given 15 min before induction. In the operating theatre women were positioned supine on the operating table with 15° firm rubber wedge under the right hip to effect left uterine displacement. A slow 500 mL intravenous (i.v.) infusion of lactated Ringer's solution was given to all subjects over 20 min.

Subjects were monitored with electrocardiography, noninvasive blood pressure, pulse oximetry (SpO_2), and end-tidal carbon dioxide ($EtCO_2$) and isoflurane concentrations. After pre-oxygenation for 5 min, rapid-sequence induction was performed with propofol 1.5-2 mg.kg^{-1} followed by suxamethonium 1.5 mg/kg after loss of verbal response. Cricoid pressure was applied after loss of consciousness and was released after correct placement of the tracheal tube had been confirmed by the presence of an $EtCO_2$ and bilateral breath sounds by auscultation.

After tracheal intubation, subjects were allocated randomly to two groups by drawing sequentially numbered sealed opaque envelopes containing a software-generated randomization code (Random Allocation Software, version 1.0.0, Isfahan University of Medical Sciences, Isfahan, Iran). The parturients in the placebo group (n = 183) received sublingual two moistened white coated placebo tablets which looked identical in size, color, and packing to misoprostol tablet. In the misoprostol group (n = 183), sublingual misoprostol was given by putting two moistened tablets of misoprostol (400 μg) (Misotac®, Sigma Pharmaceutical Industries, Egypt) (200 μg. tablet^{-1}) under the tongue and allowing them to dissolve. Anesthesiologists who gave the anesthetics and study tablets were blinded to the study randomization and were not involved in collecting of the patients' data. All staff in the operating room was unaware of the randomization code.

Anesthesia was maintained with 0.5-0.7 MAC of isoflurane with nitrous oxide 50% in oxygen to maintain the heart rate and blood pressure within 20% of baseline values. Neuromuscular block was maintained with vecuronium 0.06 mg.kg^{-1}. The lungs were ventilated using a tidal volume of 8 mL.kg^{-1}, an inspiration-expiration ratio of 1: 2, and at a respiratory rate necessary to maintain an $EtCO_2$ of 30-35 mm Hg. Induction to delivery (I-D) times was recorded using a stopwatch.

After the umbilical cord was clamped, a 10-unit infusion of oxytocin in 500 mL of Lactated Ringer's solution was started. Intravenous midazolam 0.05 mg.kg^{-1} and fentanyl 2.0 μg.kg^{-1} were given and end-tidal concentration of the nitrous oxide was increased to 70%.

The obstetrician who was blinded to the study group, assessed the uterine tone by palpation every three minutes after delivery of the placenta and rated the degree of uterine contraction on a 10 cm visual analogue scale (VAS – zero: well contracted; 10: completely relaxed). If uterine tone remained unsatisfactory after 3 min, an additional 5-unit bolus of oxytocin was administered.

All neonates were assessed by a pediatrician unaware of the randomization code as regarding their Apgar scores at 1 and 5 min, arterial blood pressure, heart rate, temperature and arterial oxygen saturation.

At the end of surgery, isoflurane and nitrous oxide were discontinued, residual neuromuscular block was antagonized and the patients were extubated. Postoperative analgesia was achieved with morphine, tramadol and paracetamol.

Uterine tone was assessed after delivery of placenta, after infusion of oxytocin, at skin closure and 2 hours after delivery. Intraoperative blood loss was assessed by measuring blood in the suction bottle minus the sonographically estimated amniotic fluid volume, visual estimate of blood on floor and weighing the used towels, linens, and swabs using an electronic scale with subtraction of their previously known dry weight, assuming that 1 mL of blood weighs close to 1 gram, the balance in grams was assumed to be the total blood loss in mL [20]. Postoperative blood loss was estimated as previously by weighing of the bed linens, gowns and perineal pad. The obstetrician who was blinded to the patient's group performed the assessment of uterine tone and subjective measurement of perioperative blood loss. Another blinded investigator calculated the estimated blood loss (EBL) as following; calculated maternal blood volume (ml) (EBV) x [preoperative hematocrit – postoperative hematocrit] / preoperative hematocrit, where EBV measured as shown in the following formula; (0.75 x {[maternal height (inches) x 50] + [maternal weight in pounds x 25]}) [21]. Number of patients received oxytocin, haematocrit values before and 48 h after surgery, subjective estimated total blood loss, transfusion requirements, Apgar scores at 1 and 5 min, and the presence of postoperative side effects such as nausea and vomiting, diarrhea, abdominal pain, pyrexia, and shivering were recorded.

Statistical analysis

Data were tested for normality using Kolmogorov-Smirnov test. Repeated measure analysis of variances was done. Unpaired Student's *t* test was used to compare the parametric values in the two groups. Mann-Whitney U test was performed to compare the non-parametric values of the two groups. Chi-square test was used for categorical data. Linear regression served to analyze the correlation between the estimated blood loss (EBL) (independent variable) and the secondary endpoint; namely, VAS for uterine relaxation (dependent variables). Data were expressed as frequency, mean ± SD, percentage or median (range). A value of $p < 0.05$ was considered to represent statistical significance.

RESULTS

A total of 382 patients were screened for eligibility, of them 366 patients completed the study; 187 patients in the placebo group and 179 in the misoprostol group. Four patients in the placebo group and 12 patients in the misoprostol group were excluded from the study due to loss to follow-up or missed preoperative hematocrit data. Maternal age, weight, height, gestational age, I-D time, duration of anesthesia, and birth weight were similar in both study groups (Table I).

Table I – Patient Data

	Placebo group (n = 187)	Misoprostol group (n = 179)
Age (years)	26.5 (16.5)	27 (19)
Weight (kg)	77.8 ± 12.22	79.1 ± 13.56
Height (cm)	160.9 ± 9.17	162.3 ± 7.24
Gestational age (weeks)	38.0 ±1.33	37.3 ±1.65
Induction to delivery time (min)	8.7 ± 2.54	9.1 ± 2.13
Duration of anesthesia (min)	60.1 ± 14.79	53.6 ± 11.82
Birth weight (kg)	3.2 ± 0.45	3.5 ± 0.30

Data are presented as median (range) and mean ± SD.

There was no perioperative changes in heart rate and blood pressure values in the two groups (data were not shown).

Patients who received misoprostol showed lower VAS for uterine relaxation after delivery of placenta ($p < 0.001$) and after infusion of oxytocin ($p < 0.02$) (Table II).

Table II – Outcome Data

	Placebo group (n = 187)	Misoprostol group (n = 179)
VAS assessment of uterine relaxation		
After placental delivery	6 (4 – 9)	0 (0 – 4) *
After oxytocin infusion	1 (0 – 6)	0 (0 – 7) †
At skin closure	0 (0 – 5)	1 (0 – 4)
Postoperative	1 (0 – 5)	1 (0 – 5)
Patients needed supplementary oxytocin *n.*(%)	52 (27.8%)	12 (6.7%) *
Cumulative supplementary oxytocin (IU)	20 (5 – 60)	5 (5 – 10) *
Hematocrit (%):		
pre-op	33.5 ± 3.88	34.2 ± 4.16
48 h post-op	30.0 ± 3.47	33.2 ± 3.79 *
Intra-operative blood loss (mL)	524 ± 119.96	222 ± 89.50 *
Postoperative blood loss (mL)	372 ± 107.41	107 ± 49.62 *
Total perioperative blood loss (mL)	894 ± 160.91	324 ± 97.44 *
Estimated blood loss (mL)	708 ± 204.32	201 ± 383.14 *
Patients received blood transfusion (n.)	11 (5.9%)	0 (0%) *
Apgar score		
1 min	8 (6 – 9)	8 (6 – 10)
5 min	9 (8 –10)	10 (8 –10)

Data are presented as median (minimum-maximum), n (%) or mean ± SD.
* $p < 0.001$ and †$p < 0.02$ compared with the placebo group.

The misoprostol group had significantly fewer number of patients receiving supplementary oxytocin, less cumulative use of oxytocin, greater hematocrit levels at 48 hours after surgery, less subjective intraoperative, postoperative and total blood loss than the placebo group ($p < 0.001$) (Table II). Additionally, the estimated blood loss and the need for blood transfusion were significantly lower in the misoprostol group than the placebo group (Table II).

Linear regression analysis revealed significant positive correlations between the estimated blood loss after cesarean delivery and VAS for uterine relaxation (correlation coefficient of 0.507) ($p < 0.001$).

Apgar scores at 1 and 5 min (Table II) and neonatal cardiovascular status were similar in the two groups.

The frequency of the nausea and vomiting, diarrhea, abdominal pain, pyrexia and shivering were shown in Table II. Number of patients who developed shivering was significantly greater in the misoprostol group than in the placebo group ($p < 0.05$) (Table II).

Table III – Postoperative Complications

	Placebo group (n = 187)	Misoprostol group (n = 179)
Nausea and vomiting	12 (6.4%)	16 (8.9%)
Diarrhea	0 (0%)	2 (1.1%)
Abdominal pain	13 (6.9%)	24 (13.4%)
Pyrexia	8 (4.3%)	16 (8.9%)
Shivering	6 (3.2%)	17 (9.5%) *

Data are presented as n (%).
* $p < 0.05$ compared with the placebo group.

DISCUSSION

There are several risk factors for postpartum hemorrhage after cesarean delivery [22]. Volatile anesthetics at clinically relevant concentrations greater than 0.8-1.0 MAC, which would provide adequate anesthetic depth, significantly reduces the oxytocin-induced contraction of uterine smooth muscle [23].

Strong evidences exist in support of the efficacy of misoprostol in reducing the postpartum blood loss after cesarean delivery [11-17].

The present study demonstrated that the preoperative use of sublingual 400 μg of misoprostol during isoflurane anesthesia for cesarean delivery was associated with significantly less perioperative bleeding, inhibited isoflurane-induced uterine smooth muscle relaxation, higher hematocrit values, comparative neonatal outcome, and higher incidence of shivering than did those in the placebo group.

On the basis of the existing evidence, we chose sublingual route of administration of misoprostol being associated with shorter times, to increase in uterine tone (10.7-11.5 min) [24], to peak plasma level (26 min) [18] and greater bioavailability [25], compared with other routes of administration. Additionally, we used single dose of sublingual misoprostol in dose of 400 μg as an effective dose to increase the uterine tone [18,24] and reduce blood loss after cesarean delivery, compared with lower ineffective doses (100-200 μg) [14,16,26], whereas the safety of larger doses larger than 600 μg poses many harmful concerns [27].

Similar to others [11-17], the present study demonstrated significant reduction in the estimated blood loss after cesarean delivery by 71.6% with the preoperative use of sublingual misoprostol of 400 μg. This is partially related to the noted significant positive correlation with uterine relaxation through antagonizing of the inhibitory effects of isoflurane on uterine smooth muscles through rise in free calcium. Therefore, we reported, in similar to other investigators, significant increase in uterine tone after the use of sublingual misoprostol [18,24].

Estimation of blood loss after cesarean delivery is a difficult issue, as visual estimation of blood loss is unreliable [28-29] and the mean blood loss is underestimated by the anesthetists as compared to the obstetricians [30]. We used, in the present study, a modified version of the formula to increase the reliability of the calculation of estimated blood loss [21], even this lacks significant relationship with coagulation parameters measured by thromboelastography [31].

In the present study, the preoperative use of sublingual misoprostol was associated with greater hematocrit levels and less need for transfusion after cesarean delivery. Some investigators reported similar less decrease in hematocrit values [13] whereas others [16,17] failed to find similar changes, which may be attributed to the use of lower dose of 200 μg of misoprostol and the smaller size of the studied population.

We found no adverse effects of neonatal outcome, as assessed by Apgar scores and vital signs after the preoperative use of sublingual misoprostol for cesarean delivery, and none of the mothers showed perioperative hemodynamic instability.

Gastrointestinal disturbances, shivering and fever are the most common side effects of misoprostol treatment. In the present study, there was no difference between the studied groups except in the occurrence of shivering after the use of sublingual misoprostol during cesarean delivery under isoflurane anesthesia. Others reported high fever may be because of the higher and the frequent dosing of misoprostol [11,32].

We believe that this trial has internal validity because of the random allocation of the studied population and the sample size was calculated according to the primary outcome of our hypothesis.

The present study has some limitations. First, someone may argue that the use of higher than 0.5 MAC of isoflurane in 50% N_2O during elective cesarean delivery may induce further uterine relaxation and increase postoperative bleeding. Indeed, we used 0.5-0.7 MAC of isoflurane which may likely provide adequate depth of anesthesia for cesarean delivery [33]. Additionally, the estimated blood loss after cesarean delivery in the present study is comparable with that reported by others [12-13]. Second, we did not monitor the depth of anesthesia

due to shortage of bispectral index and entropy monitors at our centre at the time of recruitment of the studied population. The use of such monitors would reduce the needed MAC of isoflurane with advantageous less inhibitory effects on uterine smooth muscles. Third, we did not use either gravimetry or photometry for measurement of postpartum blood loss. However, we combined both subjective and objective methods to increase the reliability of the measured blood loss.

Further multicenter trials are needed to test the efficacy and safety of different routes and doses of misoprostol on the uterine tone and postoperative blood loss after cesarean section under sevoflurane, desflurane and isoflurane anesthesia.

In conclusion, preoperative administration of sublingual misoprostol 400 μg is safe and effective in attenuating the maternal bleeding and uterine atony from isoflurane anesthesia for cesarean delivery.

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