The efficacy of intrauterine misoprostol during cesarean section in prevention of primary PPH, a randomized controlled trial


To cite this article: Mahmoud Alalfy, Yossra Lasheen, Hossam Elshenoufy, I. M. Elzahaby, Heba W. Kaleem, Heba El Sawah, Ahmed Azkalani, Waleed Saber & Ahmed S. S. A. Rashwan (2018): The efficacy of intrauterine misoprostol during cesarean section in prevention of primary PPH, a randomized controlled trial, The Journal of Maternal-Fetal & Neonatal Medicine, DOI: 10.1080/14767058.2018.1519796

To link to this article: https://doi.org/10.1080/14767058.2018.1519796

Accepted author version posted online: 03 Sep 2018.
Published online: 26 Sep 2018.

Submit your article to this journal

Article views: 10

View Crossmark data
The efficacy of intrauterine misoprostol during cesarean section in prevention of primary PPH, a randomized controlled trial


aReproductive health and family planning department, National Research Centre (Egypt), Giza, Egypt; Aljazeerah Hospital, CAIFM, Egypt; bDepartment of Obstetrics and Gynecology, Faculty of Medicine, Cairo University, Cairo, Egypt; cDepartment of Obstetrics and Gynecology, Faculty of Medicine, Cairo University, Cairo, Egypt

ABSTRACT

Background: Postpartum hemorrhage is the leading cause of maternal mortality worldwide.

Aim: To compare the incidence of postpartum hemorrhage in women eligible for elective cesarean section (CS) delivery when using intrauterine misoprostol added to oxytocin versus oxytocin alone.

Design, Setting, Participants: This parallel randomized controlled trial study was conducted in two institutions in Egypt (Kasralainy and Aljazeerah hospital) 0.300 women eligible for elective CS delivery were enrolled in the study.

Interventions: Before randomization, all women received the same preparations. After randomization; in the study group (N = 150), intrauterine misoprostol was used after placental delivery. In the control group (N = 150), the routine oxytocin alone was used.

Results: Both groups were comparable (p-value >.05) with regard to the age, BMI, and gestational age as well as hemoglobin and hematocrit levels. The incidence of postpartum hemorrhage was significantly lower (p = .018) in the study group (1.33%) than the control group (6.67%). The absolute risk reduction was 5.3% (CI 95%: 0.8–10.6%) with a relative risk of 0.20 (CI 95%: 0.05–0.90) and number needed to treat (NNT) 19 (CI 95%: 125–9). Moreover, the needs for a blood transfusion, extra uterotonics or additional interventions were significantly lower in the study group than in the control group (p < .05). All the three parameters of blood loss ie the mean blood loss, and the mean reductions of hemoglobin and hematocrit levels were significantly (p-value <.05) lower in the study group (mean and SD) (442.59 and 151.33 mL, 0.46 and 0.3 g/dL, and 0.84 and 0.56%), respectively than in the control group (591.01 and 287.97 mL, 1.2 and 1.39 g/dL, and 3.47 and 3.52%), respectively. Adverse events were comparable between groups; these were fever, nausea, and vomiting and shivering.

Conclusion: Intrauterine misoprostol (400 mg) when added to oxytocin is safe and effective in decreasing the incidence of postpartum hemorrhage (PPH) and reducing the amount of postpartum blood loss in case of elective CS delivery.

Introduction

Globally, postpartum hemorrhage (PPH), the prominent reason for maternal deaths (one-quarter of maternal deaths) has a prevalence rate of 6–10.8% [1–3]. More than one-third of all maternal mortality in Asia and Africa are due to PPH [4].

The average blood loss in PPH is variable according to the type of delivery; in vaginal delivery (500 ml of blood or more), cesarean section (CS) delivery (1000 ml or more), and in an emergency hysterectomy, it was 3500 ml [5]. In the last 30 years, many research studies and efforts have been done to improve the preventive measures for PPH which finalized in 2012 by the addition of misoprostol as an alternative for oxytocin [1].

Misoprostol, a prostaglandin E1 (PGE1) analog, selectively binds to prostanoid receptors (EP-2/EP-3). Its efficacy as a stimulant of the myometrium of the pregnant uterus has been shown has been shown in many research studies [6]. In addition, its administration, orally or rectally, has been demonstrated its efficacy in preventing PPH. It is considered as an effective alternative to other conventional ecbolic drugs [7]. Moreover, pharmacokinetic research studies showed that it has a higher bioavailability after sublingual
administration than after oral or vaginal administration [8]. Thus, its administration sublingually for the prevention of PPH has been evaluated and proved its effectiveness [9].

To the best of our knowledge, there is only one research study by QuirogaDíaz et al. studied the effect of the intrauterine use of misoprostol (800 mg) versus placebo for the prevention of PPH after CS delivery [10].

Thus, the rationale intended for this parallel randomized controlled study was to test the hypothesis that adding intrauterine misoprostol (400 mg) to the conventional oxytocin 10 IU will decrease the incidence of PPH in CS delivery more than that reduction achieved by the traditional oxytocin drip alone and will reduce the amount of blood loss.

Materials and methods

**Study design**

Pregnant women were enrolled in controlled, randomized, parallel trial (ClinicalTrials.gov identifier: NCT03390010). The study was conducted in the delivery rooms of Cairo University Hospital and Aljazeerah Hospital, Egypt. Ethical committee approval was obtained in October 2017. Then the study was approved for registration in clinicaltrials.gov in December 2017 after which actual enrollment of patients in the study commenced and finished in February 2018.

The study conformed to the Declaration of Helsinki principles and following the Medical Research Involving Human Subjects Act. The Bio-Medical Research Ethical Committee of Cairo University and the ethical committee of Aljazeerah hospital approved the research. The purpose of the study was explained in simple and lay Arabic language to all women before their enrollment in the study, and an informed consent form was signed by and obtained from all those enrolled women.

Pregnant women meeting all of the following criteria were considered for enrollment: aged 18–35 years, primigravida, singleton pregnancy, full term, and candidate for elective cesarean section delivery at term, and had their delivery in the two centers during the period of the study.

Women presenting with any of the following were excluded from the study: antepartum hemorrhage in this pregnancy, preterm or post-term delivery, severe anemia with HB <8 mg/dL, and history of preexisting maternal hemorrhagic conditions such as factor 8 or 9 deficiency or von Willebrand’s disease. Also, women with fibroids, placenta praevia or medically complicated pregnancy were excluded.

**Interventions in both groups**

The two groups were subjected to the same preparation. Both groups received oxytocin drip (10 IU). For all women in the study group only (150 women) intrauterine misoprostol tablet (400 mg) was used. After delivery of the placenta and swabbing the cavity, the surgeon places a tablet in the uterine cavity at the fundus while suturing the first layer of the uterus.

**Randomization and blinding**

Before the trial, computer-generated randomization schedules were generated and placed in sequentially numbered sealed opaque envelopes.

Block randomization with a block size of four was used with a 1:1 ratio of both groups (study and control groups). Women were recruited, gave consent and opened the randomization envelopes in early labor. Also, the woman was recruited before revealing the allocation. Sealed opaque envelope method was used for the allocation. The allocation was blind to both recruiter and participant.

**Procedures**

All pregnant women were subjected to detailed history (obstetric, medical, and surgical), complete general examination to exclude the presence of any disorders. Obstetrical examinations were made systematically according to the centers’ protocols. Hemoglobin (HB) and hematocrit levels were made before and 24 h after delivery. The vital signs were observed intraoperative and every 30 min after.

For each patient, the amount of blood loss was estimated using the standardized visual estimation method and corrected by calculating the volume of blood loss during CS delivery and 6 h postoperatively. The whole blood loss equals the total loss of blood during CS delivery which calculated by adding the volume of the suction bottle to that blood-soaked sponges (weighting method), all these were added to the volume of blood loss after CS which was measured by using blood collection drape [11–14].

All women were followed up postoperatively for 24 h then dismissed.
Outcome measures

The primary outcome measure was the estimation of the amount of blood loss during and after cesarean delivery following administration of intrauterine misoprostol Plus intravenous oxytocin compared to intravenous oxytocin alone and calculation of incidence of PPH (>1000 ml blood loss) within the first 6 h of labor in both groups. The secondary outcome measures were the need for blood transfusion, the need for any additional ecobic drugs, and the changes in hematocrit and HB in both groups after delivery, and the incidence of side effects.

We used to manage PPH according to this protocol as follows:

Management includes the following parallel steps which are call for help with call for anesthesia and obstetrics and gynecology consultants, communication, resuscitation, monitoring investigation, and arresting bleeding.

Resuscitation is tried by restoration of both blood volume and oxygen carrying capacity, with two wide bore 14 gauge intravenous lines, a blood sample for full laboratory investigations. A high concentration of oxygen is taken. Pulse rate, blood pressure, oxygen saturation using oximeter, ECG, and automated blood pressure recording, considering central and arterial lines, Foley’s catheter to measure urine output and a record chart for fluid balance, blood, blood product, and procedures. Blood should be transfused as soon as available, till then, 3.5 L of warmed crystalloid Hartmann’s solution (2L) and/or colloid (1–2L) infused. Recombinant factor VII, a therapy should be based on the results of coagulation. Compatible blood is the best fluid to replace and must be transfused as soon as it is ready [15].

The arrest of bleeding is tried according to the cause, there may be one or more causes for PPH either atone, traumatic, retained products of conception or thrombin. The most common is uterine atony. Uterine massage, bimanual uterine compression are started to stimulate contraction, administration uterotonics drugs (oxytocin, ergometrine, misoprostol, carboprost), until the bleeding stops.

Thorough examination is made to exclude any retained parts, any trauma and if proved, management is started with removal of retained products or suturing the laceration is made.

If the pharmacological method fails to control bleeding in case of atonic PPH, exclusion of other or additional causes by undertaking clinical examination in theater and the next intervention is the mechanical method of controlling the bleeding by balloon catheter tamponade is instituted before considering surgical procedures [15].

Mechanical methods by Balloon tamponade: we used to put a Bakri balloon. Cases with negative balloon tamponade test and failure to arrest bleeding by intrauterine balloon tamponade in uterine atony need immediate surgical interventions [16].

Surgical treatment with bilateral uterine artery ligation, 90% of the uterus blood supply in pregnancy comes from these vessels, uterine compression sutures: B-Lynch sutures, these compression sutures exert a mechanical compression of the uterine vascular sinuses without occluding either uterine arteries or uterine cavity [17].

If this measure fails to control bleeding, the next step is ovarian artery ligation. If failed to control, then bilateral ovarian artery ligation. If this also fails to control then the next step is internal iliac artery ligation. This procedure is always made by the most senior consultant in the hospital [18].

Peripartum hysterectomy can be total or subtotal, it is done as a last resort when all other methods to control PPH fail. Subtotal hysterectomy is the choice unless there is a trauma to cervix or lower uterine segment [19].

Transfusion protocol is vital in management of PPH [20]. Early use of blood products is generally required to avoid dilutional coagulopathy. We used to give packed blood cell and fresh frozen plasma in a ratio of 1:1 and 1:2 and targeted use of platelets in an effort to avoid dilutional coagulopathy [21].

Statistical analysis and sample size justification

A sample size calculation was estimated to calculate the number of women needed in each group. Reference to Vimala et al. [22], the mean blood loss with the use of oxytocin was 974 ml with a standard deviation of 285 ml. We assumed that the intrauterine misoprostol 400 mg is more effective than oxytocin in reducing the amount of blood loss by 124 ml. Thus, 111 women will be needed in each group with 90% power ($\beta = 0.1$) at 5% significance ($\alpha = 0.05$) to detect such a difference. So, the total needed sample is 222 rounded to 300 to allow for any dropouts.

All statistical analyses were made with the intention to treat analysis method. All statistical tests were made using a significance level of 95%. $p$-values <.05 was considered statistically significant. SPSS software (version 20.0, SSPS Inc, Chicago, IL, USA) was used for the statistical analyses. Data were presented as
Assessed for eligibility (Screened) N = 445

Enrolled to the study N = 300

Randomized N = 300

Study group N= 150

Control group N= 150

Intent to treat N= 15

Per Protocol N= 15

Figure 1. CONSORT diagram.

Table 1. Patients’ characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Study group N = 150</th>
<th>Control group N = 150</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (years)</td>
<td>26.26 (3.24)</td>
<td>25.85 (3.32)</td>
<td>.661</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>21.85 (2.01)</td>
<td>22.71 (2.01)</td>
<td>.14</td>
</tr>
<tr>
<td>Gestational age</td>
<td>38.85 (1.02)</td>
<td>38.38 (0.96)</td>
<td>.108</td>
</tr>
</tbody>
</table>

(mean ± SD) for continuous variables and as frequency and percent for categorical variables. Comparisons between groups were made using a chi-square test for categorical variable and the independent t-test for the continuous variables. For the analysis of the primary outcome variable, we calculated the relative risk (RR) with 95% confidence interval, the absolute risk reduction (ARR), the relative risk reduction (RRR) and the number needed to treat (NNT).

Results

Four hundred forty-five (445) singleton pregnant women at term who came to the center and were eligible for elective cesarean section delivery were asked to participate in the study. Eighteen women declined to participate, and 127 women did not meet the inclusion criteria, leaving 300 eligible for randomization with 150 assigned to each group. None were excluded after randomization. The dispositions of these women are shown in Figure 1.

Baseline characteristics

Both the study and the control groups were comparable with regard to their baseline characteristics. There was no statistically significant difference (p > .05) between the two groups regarding the age, BMI, as well as gestational age, as shown in Table 1.

Postpartum hemorrhage

A total of 12 cases had postpartum blood loss more than 1000 ml. Postpartum hemorrhage was significantly lower (p = .018) in the study group than in the control group. In the study group, two cases (1.33%) have PPH whereas, in the control group, 10 (6.67%) had suffered PPH incident. The ARR was 5.3% (CI 95%: 0.8–10.6%) with RR of 0.20 (CI 95%: 0.05–0.90) and number needed to treat (NNT) 19 (CI 95%: 125–9), as shown in Table 2. All of PPH cases were subjected to the standard protocol of management of PPH in the center as described above.
None of the two PPH cases of the study group needed a blood transfusion; however, 4 (2.67%) of the control group needed it \((p = .043)\). Extra uterotonics were needed in 5 (3.33%) cases of the study group versus 16 (10.67%) in the control group, \((p = .012)\). Only one case (0.67%) of the study group needed intervention versus seven (4.67%) cases in the control group, \((p = .033)\). Interventions were Bakri balloon insertion, uterine artery ligation, B. Lynch suturing and internal artery ligation.

Estimated blood loss was significantly \((p < .001)\) lower in the study group 442.59 (151.33) mL than in the control group 591.01 (287.97) mL with a mean difference of 148.42 (26.56) mL.

### Changes in hematological parameters

Antepartum HB level and hematocrit value were comparable between both groups \((p > .05)\); it was mean (SD) 11.61 (0.89) g/dL and 34.42 (3.86%) in the study group and 11.51 (1.02) g/dL and 33.04 (4.21%) in the control group. However, the postpartum HB level was significantly \((p = .011)\) higher in the study group 11.15 (0.89) g/dL than in the control group 10.31 (1.27) g/dL. The mean reduction of HB level was significantly \((p = .014)\) lower in the study group 0.46 (0.3) than in the control group 1.2 (1.39). Moreover, postpartum hematocrit level was significantly \((p = .003)\) higher in the study group 33.58 (3.81%) than in the control group 29.57 (5.09%). This was reflected as the mean reduction of hematocrit was significantly \((p = .001)\) lower in the study group 0.84 (0.56) than in the control group 3.47 (3.52), as shown in Table 3.

### Adverse events

Fever was encountered in one case (0.67%) of the study group and two cases (1.33%) of the control group, \((p = .566)\). Nausea and vomiting were encountered in three cases (2.00%) of the study group and five cases (3.33%) of the control group, \((p = .475)\). Shivering was encountered in one case (0.67%) of the study group and two cases (1.33%) of the control group, \((p = .566)\).

### Discussion

Because of the mortality and morbidity of PPH, finding more methods either pharmacologic or nonpharmacologic to such a tragic event should be exceedingly invigorated. Every attempt should be done towards the prevention of PPH. Many uterotonics have been evaluated for years for the prevention of PPH. Of course, the use of oxytocin did such, but in spite of that, still, about half a million deaths each year from pregnancy and delivery complication most of them are in the Third World. PPH comes as a leading cause of the maternal loss. Needless to say, that blood loss in women whose their iron stores are already severely depleted have more morbidity and mortality.

This randomized controlled study was conducted to test the hypothesis that the use of intrauterine misoprostol (400 mg) will reduce the incidence of PPH as well as decrease the amount of blood loss than when using oxytocin drip alone in cases of CS delivery.

It was quite evident from this study that adding intrauterine misoprostol will further reduce the incidence of PPH where the ARR was 5.3% (CI 95%: 0.8–10.6%) with RR of 0.20 (CI 95%: 0.05–0.90) and NNT 19 (CI 95%: 125–9). That resulted in significantly improved hematological parameters with less blood loss and better postpartum hematocrit value in the study group than that in the control group. Furthermore, the mean value of HB drop was lower in the study group than in the control group after delivery. That reduced the need for blood transfusion, extra uterotonics, and more interventions.

The concept of using intrauterine misoprostol for prevention of PPH was mentioned by QuirogaDiaz et al. However, they used 800 mg in their study on 200 patients [10].

In the current study, the dose 400 mg was used among 300 patients. The results of QuirogaDiaz et al. study are in agreement with the current study as

<table>
<thead>
<tr>
<th>Table 2. Incidence of postpartum hemorrhage.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study group ( N = 150 )</td>
</tr>
<tr>
<td>Postpartum hemorrhage</td>
</tr>
<tr>
<td>No Postpartum hemorrhage</td>
</tr>
<tr>
<td>PPH rate in the study group</td>
</tr>
<tr>
<td>PPH rate in the control group</td>
</tr>
<tr>
<td>Relative risk (RR)</td>
</tr>
<tr>
<td>Relative risk reduction (RRR)</td>
</tr>
<tr>
<td>Absolute risk reduction (ARR)</td>
</tr>
<tr>
<td>Number needed to treat (NNT)</td>
</tr>
</tbody>
</table>

-PPH is defined as excessive bleeding in the first 24 h post-cesarean section with estimation of blood loss volume of 1000 ml or more. [5,23].
misoprostol diminished the necessity of additional uterotonics and the reduction in hemoglobin and hematocrit. They also reported few adverse events. There are several studies about the efficacy of misoprostol either orally or sublingually for reducing the amount of postpartum blood loss. Some showed that misoprostol 400 mg is as effective as or more effective as oxytocin or syntometrine [6,15,24–28].

Conde-Agudelo et al. conducted a systematic review and meta-analysis of the usage of misoprostol to reduce the intraoperative and the postoperative hemorrhage during CS delivery. Among the 17 studies included (3174 women), seven were for misoprostol versus oxytocin and eight for misoprostol plus oxytocin versus oxytocin alone [29].

They found that there were no significant differences in the intraoperative and the postoperative hemorrhage between sublingual or oral misoprostol, and the oxytocin. However, they found that rectal misoprostol, when compared with oxytocin, had a significant reduction in the intraoperative and the postoperative hemorrhage [29].

On the other hand, when sublingual misoprostol was combined with oxytocin, and compared with oxytocin alone, they found a significant reduction in the mean hematocrit reduction and the use of extra uterotonics. Moreover, the results of their systematic review revealed that when compared to oxytocin alone, buccal misoprostol added to oxytocin reduced the use of extra uterotonics. In addition, rectal misoprostol when added to oxytocin decreased the intraoperative and the postoperative blood loss, the mean fall in the hematocrit level, and the use of extra uterotonics [29].

Finally, they reported that the intrauterine misoprostol, when added to oxytocin, reduced the mean reduction in the levels of hemoglobin and hematocrit. They also reported that the rates of use of extra uterotonics, blood transfusion, and adverse events did not differ significantly between the two groups. However, they found that this one trial had a low risk of bias [29].

Also, the systematic review reported that women receiving misoprostol, either alone or combined with oxytocin, had a higher risk of pyrexia and shivering [29].

The evidence of the current study is fairly strong to prove the efficacy and safety of the intrauterine misoprostol 400 mg in the prevention of PPH in CS delivery especially when added to oxytocin. Therefore, we believe that its generalization will help to reduce the tragic effect of PPH specifically in the low developed countries.

### Conclusion

Intrauterine misoprostol (400 mg), when added to oxytocin, is effective in decreasing the incidence of PPH and reducing the amount of postpartum blood loss. Also, it reduced the need for blood transfusion, the extra uterotonic, additional intervention and with less reduction in postoperative HB level and hematocrit level when compared to oxytocin alone. Besides, it is as safe as oxytocin alone.

### Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research bioethical committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

### Informed consent

Informed consent was obtained from all the individual participants included in the study.

### Acknowledgments

We would like to acknowledge all staff members who cooperated in this research in Kasralainy Hospital and Aljazeera Hospital, also we would like to thank the persons who made the statistical analysis of the work.

### Disclosure statement

No potential conflict of interest was reported by the authors.

---

**Table 3. The mean changes in hematological parameters.**

<table>
<thead>
<tr>
<th>Study group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 150</td>
<td>N = 150</td>
</tr>
<tr>
<td>Antepartum HB (g/dL)</td>
<td>11.61 (0.89)</td>
</tr>
<tr>
<td>Postpartum HB (g/dL)</td>
<td>11.15 (0.89)</td>
</tr>
<tr>
<td>Reduction in HB level</td>
<td>0.46 (0.3)</td>
</tr>
<tr>
<td>Antepartum Hematocrit (%)</td>
<td>34.42 (3.86)</td>
</tr>
<tr>
<td>Postpartum Hematocrit (%)</td>
<td>33.58 (3.81)</td>
</tr>
<tr>
<td>Hematocrit reduction</td>
<td>0.84 (0.56)</td>
</tr>
</tbody>
</table>
ORCID

Mahmoud Alalfy  http://orcid.org/0000-0002-8429-6376

References


