Randomised Controlled Trial

Optimal dose of misoprostol combined with oxytocin for preventing postpartum hemorrhage in cesarean section: A randomised controlled trial

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Abstract

Background: The study analyzed an optimal misoprostol dosage in prevention of postpartum hemorrhage (PPH). Also evaluated the side effects that might be related to dose of misoprostol.

Material and methods: A randomised study was performed in mothers who received cesarean section. Participants were divided into 3 groups of 400, 600 and 800 μg intrauterine misoprostol insertion combined with oxytocin. Clinical characteristics, laboratory testing and operative data were collected. The primary outcome was the amount of intra-operative blood loss and side effects were assigned as a secondary outcome.

Results: There were 357 eligible cases, 119 cases in each group equally. Baseline characteristics were similar in between groups. Higher misoprostol dosage demonstrated lower blood loss. Mean blood loss was 509.1, 465.7 and 441.1 ml in the 400, 600 and 800 μg misoprostol groups respectively which were significant difference (p value 0.027). Intra-operative blood loss ≥500 ml occurred less frequently in patients receiving higher misoprostol dosage (p value 0.035). However, PPH was not identified difference between groups (p value 0.707). Nausea and vomiting were complained in less than 1% while none of the cases exhibited shivering. Pyrexia was identified in all groups, however, there was a trend towards lower dosage related to less percentage of pyrexia.

Conclusions: Either 400, 600 or 800 μg of misoprostol can prevent PPH similarly. However, the study prefers 400 μg misoprostol because of minimization the side effects.

1. Introduction

Cesarean section (CS), an operation that is performed when a vaginal delivery is not possible. The procedure can be accomplished safety in the primary care and also tertiary care hospital [1,2]. Although an amount of blood loss in CS is reported higher than normal vaginal labor [3–6], however CS still be a technique for childbirth when it is indicated [1,2]. Prior studies reported an option for reducing surgical bleeding and their results showed agreement that oxytocin prevented postpartum hemorrhage (PPH) by helping the uterine contraction [7,8]. Furthermore, administration of other uterotonic agents have been studied for more effectiveness of treating excessive blood loss [8]. Misoprostol, a prostaglandin E1 analogue, shows a good uterotonic property and less side effects which is available in worldwide even in the low resource setting [9,10]. Systematic reviews also demonstrated that misoprostol combined with oxytocin decreased an incidence of PPH significantly [8,11–13]. According to their synergistic effects which oxytocin acts immediately with short half-life while misoprostol provides sustainable efficacy of uterine contractility [14,15].

Misoprostol, in a tablet preparation, can be prescribed in different

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route including sublingual, oral, rectal and vaginal [16]. In addition, intrauterine insertion is well documented in many studies recently [9, 17,18]. While an optimal dosage of intrauterine route has not been well established, range of dosage from 400 to 800 μg were used safely [16, 19]. However, side effect such as pyrexia (body temperature (BT) ≥ 38 °C) was significant high related to higher doses (≥800 μg) of misoprostol was reported [16].

The aim of this study sought to identify the optimal intrauterine misoprostol dosage which provided maximum effectiveness of PPH control when combined with oxytocin. Additionally, also evaluated the side effects that might be related to dose of misoprostol which made mothers distress during their recovery period.

2. Material and methods

The prospective randomised controlled trial, paralleled, study was conducted at the obstetrics and gynecology unit and was reported in the line with the CONSORT guidelines [20]. The protocol of the investigation was approved by the Institutional Review Board. The registration unique identifying number (UIN) was UIN 7966 [21]. The clinical trial registration number was TCTR 20211102001. This study collected the data from pregnant women who had a singleton pregnancy with gestational age (GA) 37–42 weeks. All participants underwent emergency or elective CS according to their indications. The exclusion criteria were: 1) twin pregnancy; 2) pregnancy with obstetric hemorrhage including placenta previa; 3) abruptio placenta and vasa previa; 4) preeclampsia with hemolysis, elevated liver enzyme and low platelets syndrome (HELLP); 5) pregnancy with coagulopathy or thrombocytopenia or blood dyscrasias; 6) pregnancy who had a history of prostaglandin allergy or received medications which could cause severe drug interaction to prostaglandins and 7) pregnancy with term false labor pain.

2.1. Sample size calculation

The sample size for the present study was calculated using a power analysis targeting a 90% chance of detecting an effect. Power analysis was based on a pilot study [9] where mean and standard deviation of intra-operative blood loss were collected from patients who received intrauterine misoprostol plus intravenous oxytocin and those who received intravenous oxytocin only. The resulting sample size was 110 for each group.

2.2. Participants and blinding

All participants were provided detailed information about the study by the researcher and completed the written informed consent. Baseline clinical characteristics were collected as follows: maternal age, GA, gravida and parity, indication for CS and risk factors for CS such as elderly gravida (maternal age ≥35 years old), teenage pregnancy (maternal age <20 years old), previous CS and co-morbid disease. Hemoglobin (Hb) and hematocrit (Hct) values were recorded pre-operatively. Data during peri-operative period included anesthetic type, type of skin incision, birthweight, additional uterotonic agents, intra-operative blood loss and 24 h of post-operative Hb and Hct levels were also recorded. In addition, requirement of blood transfusion and clinical manifestations of misoprostol side effects included nausea/vomiting, shivering and pyrexia were documented.

Eligible pregnant women were randomised with a 1:1:1 allocation ratio to receive a treatment intervention. The simple randomization was performed by a blinded midwifery who prepared a non-label dosage of misoprostol package for operation. Each woman, also blinded side, was assigned the different dose of intrauterine misoprostol insertion as follows: 400 μg, 600 μg and 800 μg. Nursing care team who responsible for routine postpartum care also could not identified the drug dosage.

2.3. Intervention

In this setting, all obstetricians performed the similar standard CS technique and also used the same uterotonic agents. All pregnant women who were indicated for CS received oxytocin combined with misoprostol. The dose of oxytocin was 20 units plus 0.9% normal saline solution 1000 ml starting with 250 ml intravenous within 10 min (0.5 units/min) and followed by 120 ml/h (0.04 units/min) for 6 h. And after placenta was delivered, intrauterine misoprostol by random dosage was inserted at cornual part bilaterally by surgeon. However, additional uterotonic agents might be prescribed by the obstetrician who performed an operation based on clinical assessment during operation period and recorded by anesthesiologist.

2.4. Outcome assessment

The primary outcome was volume of intra-operative blood loss that was calculated by prior study techniques [9] which was compatible with the American College of Obstetricians and Gynecologists (ACOG) recommendation [22]. Measurement the amount of blood loss in the suction canister was started immediately after the baby was born until after placenta delivery [22] plus the difference in weight of abdominal swabs and gauzes before and after operation, where 1 g of weight difference equals to 1 ml of blood loss. Furthermore, vital signs post-operatively, required blood transfusion, changing of Hb and Hct levels between pre and 24 h post-operation were recorded. All described parameters were used to evaluate several degrees of blood loss and PPH. The term of PPH was classified following ACOG revitalize program that defined as a cumulative blood loss of greater than or equal to 1000 ml or blood loss accompanied by signs or symptoms of hypovolemia within 24 h after the birth process (includes intrapartum loss) regardless of route of delivery [23].

Secondary outcome was side effects of misoprostol. The following parameters that included 1) pyrexia (BT ≥ 38 °C), hyperpyrexia (BT ≥ 40 °C) (2) nausea/vomiting/shivering (3) receiving of antiemetic drugs were evaluated post-operatively. Close monitoring was performed within 6 h after surgery and as a routine postpartum care until discharge date.

2.5. Statistical analysis

Baseline characteristics were summarized as percentages or means ± standard deviation (SD). Differences between treatment groups were compared using chi-squared tests or Fisher’s exact tests based on expected cell counts for categorical variables. For continuous variables, the differences between treatment groups were analyzed using analysis of ANOVA or Kruskal-Wallis tests. The Bonferroni approach was used to adjust for multiple comparisons on pairwise tests. All analyses were performed using Stata software version 14.2 (StataCorp, College Station, TX). All tests were two-tailed with alpha set at 0.05.

3. Results

A total of 413 pregnant women were screened and 357 cases were compatible with the study’s inclusion criteria. A randomization was performed into 3 treatment groups according to the dosage of intrauterine misoprostol included 400 μg (n = 119), 600 μg (n = 119) and 800 μg (n = 119) (Fig. 1). The baseline data as follows: maternal age, GA, gravida and parity, indication for CS, risk factors for CS, anesthetic type, type of skin incision, birthweight and pre-operative laboratory showed similarity in all 3 groups (Table 1).

Mothers who received higher misoprostol dosage demonstrated lower blood loss (Table 2 and Fig. 2). Mean blood loss was 510.0 ml, 465.7 ml and 441.1 ml in the 400 μg, 600 μg and 800 μg misoprostol groups respectively which were significant difference. A single-factor ANOVA comparing blood loss across the three groups yielded a
significant effect (p value 0.027) (Table 2). Post-hoc pairwise t-tests found that 800 μg group diminished blood loss less than 400 μg group (p value 0.004) (Fig. 2). There was a trend towards a difference in the other two pairwise comparisons (800 μg vs. 600 μg; p value 0.054 and 600 μg vs. 400 μg; p value 0.139). In addition, intra-operative blood loss ≥500 ml occurred less frequently in patients receiving higher doses of misoprostol (Table 2 and Fig. 3). There were 29.4%, 35.3% and 45.4% of the cases in the 800 μg, 600 μg and 400 μg misoprostol groups respectively. A chi-squared test confirmed that the proportion of women who had intra-operative blood loss ≥500 ml was statistical difference between groups (p value 0.035) (Fig. 3). Contrast with volume of blood loss ≥1000 ml which indicated PPH event was not identified difference between groups (p value 0.707). Even though average blood loss and blood loss volume ≥500 ml were demonstrated difference, however value of changing in Hb and Hct levels were similar among three groups (p value 0.864). Requirement of additional uterotonic agents and blood transfusion were also similar between groups (Table 2).

Side effects of misoprostol that included nausea and vomiting were complained in less than 1% of the cases. Mother who presented those symptoms did not require additional antiemetic drugs. However, small number of participants received antiemetic drugs that were prescribed by anesthesiologist peri-operatively (Table 2). On the contrary, pyrexia was identified in more than 50% of the cases in all groups. The lower percentage of pyrexia related to 400 μg misoprostol group. However, the high BT was always detected in the short duration of time within 6 h post-operatively and was corrected by conservative treatment. Only 1 case of patients in group of 600 μg and 800 μg misoprostol were reported hyperpyrexia. None of the cases exhibited shivering symptom. The good treatment outcome and safety of all mothers and their babies in this study were demonstrated.

4. Discussion

Maternal and child safety are the purpose of treatment outcome in every labor. Achievement of those goals can completely by prevention, early detection and prompt response of complications especially serious postpartum bleeding. Additionally, world health organization and united nations children’s fund recommend an early skin to skin contact with breastfeeding within 1 h after birth if it possible [24,25]. Therefore, good physical and mental health status of mother in postpartum period would be the key factors to reach the recommendation.

To our knowledge, this is the first study that analyzed the optimal dose of intrauterine misoprostol insertion. In this study, neither 400 μg, 600 μg nor 800 μg did not show any significant difference in the development of PPH. Each three different doses of misoprostol were supported by many prior literatures and all publication reported an effectiveness in reduction of PPH when combined with oxytocin [9,13,17,18]. Several comparison trails also summarized the positive impact of misoprostol 600 μg and 800 μg [9,16]. In 2020, Alafy M. et al. also published an efficacy of 400 μg of misoprostol in reduction of PPH [19]. In spite of an incidence of PPH did not difference in this study, an observation of 400 μg of misoprostol had an average volume of intra-operative blood loss higher than other groups significantly. Furthermore, the amount of blood loss between ≥500 ml and <1000 ml was more frequency recorded in low dose group. Although there was not alteration in Hb and Hct values, however, minimization of intra-operative blood loss should be considered to stabilize a hemodynamic of the mothers who might have an un-discovery underlying health problem. In addition, post-operative Hb and Hct values changing can develop and stabilize within 24–48 h after acute hemorrhage [26], and the timing of blood specimen collection might interfere with laboratory result.

The common side effect of misoprostol is pyrexia that is defined as an un-explained asymptomatic raising of body temperature [27]. Although pyrexia is self-limited and usually mild degree [28], rarely in severe form of hyperthermia [29], mother usually expresses uncomfortable and anxious. This experience will delay timing of maternal and child first contact after birth. This study reported high rate of pyrexia in all groups (52–62%) when compared to prior studies in variable doses of misoprostol [16,27,28]. However, previous randomized study trail in 2018 [9] demonstrated pyrexia in 66.7% of 800 μg intrauterine misoprostol that slightly increased than the recent study. The high percentage of pyrexia related to high dosage of misoprostol which similar to systematic review in 2019 [16]. Nausea and vomiting were also mentioned in the prior literatures of various misoprostol dosage in 0.8–23% [16,30,31] while this study trail revealed 0.8% of 400 μg misoprostol group who experience those side effects. The low percentage might be interfered by peri-operative antiemetic drugs.

Limitation of this study was an appropriated timing to measure Hb and Hct values changing. In mother who clinical stable, laboratory
Intrauterine misoprostol insertion reveals efficacy to decrease cesarean delivery excessive blood loss when combined with oxytocin. Either 400 μg, 600 μg or 800 μg of misoprostol can prevent excessive postpartum bleeding equally. Nevertheless, the study prefers 400 μg misoprostol to prevent PPH because of low dose minimizes the side effects. And also provides enhancement of maternal postpartum recovery to achieve mother and baby first contact and early breastfeeding.

5. Conclusion

Intrauterine misoprostol insertion reveals efficacy to decrease cesarean delivery excessive blood loss when combined with oxytocin. Either 400 μg, 600 μg or 800 μg of misoprostol can prevent excessive postpartum bleeding equally. Nevertheless, the study prefers 400 μg misoprostol to prevent PPH because of low dose minimizes the side effects. And also provides enhancement of maternal postpartum recovery to achieve mother and baby first contact and early breastfeeding.

Disclosure

The authors have nothing disclosure.

Data statement

The research data is confidential.

Provenance and peer review

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Registration of research studies

1. Name of the registry: Research registration for unique identifying number
2. Unique Identifying number or registration ID: UIN 7966
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Declaration of competing interest
All authors have no conflicts of interest.

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