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Prevention of Postpartum Hemorrhage with Oxytocin versus Ergometrine plus Oxytocin in the Third Stage of Labor

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ABSTRACT

Objective: To evaluate the effect of the addition of intravenous ergometrine to a standard oxytocin infusion on the blood loss during vaginal delivery.

Materials and Methods: This was a prospective, double-blined, randomized controlled trial. Three hundred and twenty-three women were randomized to receive infusion of either ergometrine 0.2 mg plus oxytocin 20 IU or oxytocin 20 IU, diluted in 1,000 ml of 5%D/N/2, immediately after delivery of the baby. The primary outcome was the estimated blood loss. The secondary outcomes included PPH, changes in hemoglobin level, the use of additional uterotonics, need for blood transfusion and adverse effects.

Results: The estimated postpartum blood loss was similar in the oxytocin–ergometrine and oxytocin groups (145 ml versus 150 ml, p=0.979). None of the women in the oxytocin–ergometrine group had PPH while one woman (0.6%) in the oxytocin group encountered this complication (p=0.498). There was no significant difference between both groups in terms of changes in hemoglobin level, use of additional uterotonics and need for blood transfusion. Hypertension was significantly more common in the oxytocin–ergometrine group than in the oxytocin group (6.2% VS 0%, p<0.001).

Conclusion: There was no difference in postpartum blood loss during vaginal delivery between oxytocin–ergometrine and oxytocin groups. Hypertension was frequently found in the oxytocin–ergometrine group. However, other adverse effects were not significantly different between both groups.

Keywords: Blood loss, ergometrine, oxytocin, prevention, adverse effects.

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Introduction

Postpartum hemorrhage (PPH), defined as a blood loss of ≥ 500 ml after delivery, is the most common complication of labor, and is the leading cause of maternal death worldwide[1, 2]. More than one-third of all maternal deaths in Thailand result from this complication[3]. Most cases of PPH are caused by uterine atony, which is preventable[4].

World Health Organization has recommended active management of the third stage of labor (AMTLS) with uterotonics, controlled cord traction, and uterine massage as standard care[5]. A major component of active management of the third stage of labor is the administration of a prophylactic uterotonic agent. Available evidence supports routine administration of oxytocin or ergot alkaloids for the prevention of PPH[6, 7]. In Thailand, oxytocin has been used by various routes of administration such as intravenous bolus, intravenous infusion and intramuscular injection[8]. The need for additional ergometrine for postpartum hemorrhage prevention were not stated clearly.

The purpose of this study was to evaluate the effect of the addition of intravenous ergometrine to oxytocin infusion on blood loss during vaginal delivery. We hypothesized that this combination of drugs would be more effective in reducing blood loss than oxytocin alone in these women.

Materials and Methods

A prospective, randomized, and double-blind trial was conducted among women undergoing spontaneous labor at Department of Obstetrics and Gynecology, Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand, from 1 October 2014 to 31 January 2015. Approval for the study was obtained from the Research Ethics Board at Faculty of Medicine Vajira Hospital and all the study subjects gave written informed consent during the first stage of labor.

The inclusion criteria were singleton pregnancy over 28 weeks of gestation, with cephalic presentation, anticipating a normal spontaneous vaginal delivery. The criteria for exclusion were multiple pregnancy, polyhydramnios, uterine fibroids, previous postpartum hemorrhage, antepartum hemorrhage, parity greater than four, previous cesarean section, severe anemia (hemoglobin level of ≤ 8 g/dL), coagulopathy, contraindications to the use of ergometrine, estimated fetal birth weight > 4,000 g. and inability to obtain written informed consent. Women who ended up having a cesarean section or instrumental delivery were also excluded from this study.

Based on a random allocation scheme derived from a computer-generated list of numbers, sealed and consecutively numbered opaque envelopes were prepared by a research assistant not involved in the study. The women were randomly allocated to one of the two study groups by opening the next available envelope just before delivery. After delivery of the baby, all participants were given intravenous infusion of 20 IU of oxytocin diluted in 1000 ml of 5% D/N/2 at a rate of 120 ml/h. Patients in the study group received intravenous injection of ergometrine 0.2 mg (1 ml), while patients in the control group received intravenous injection of normal saline 1 ml (placebo) immediately. The study drug and placebo were prepared by the research assistant not involved in the study. The obstetrician and nursing staff were all blinded to the type of injectable substance. As a part of the standard of care, controlled cord traction and uterine massage were provided to both groups by the obstetrician.

At the start of this randomized controlled trial, no other trials in the published literature had compared the oxytocin infusion plus intravenous ergometrine with oxytocin infusion alone. Therefore, we conducted a non-blinded pilot trial of 20 patients in each group. The blood loss measured was 211.5±24.5 ml and 242±43.2 ml for oxytocin plus ergometrine and oxytocin, respectively. Sample size was calculated to achieve a statistically significant difference for type-I error of 5%, a power of 80% and a potential dropout rate of 10%. Therefore, the sample size of this study was 163 women per group.

Baseline demographic and obstetric data comprisedof age, parity, BMI, partographic findings, and delivery events were recorded. Predelivery hemoglobin concentration was measured for all women on admission to the labor ward.

As visual assessment of blood loss is generally inaccurate and underestimated, this study objectively measured amount of blood loss using the blood collection drape, which was placed under the buttocks after placental delivery. Blood-soaked swabs were weighed in grams, and the known dry weight of the swabs was subtracted, this volume was added to the measured blood volume from the drape (assuming an

equivalence of 1 g to 1 ml). Blood loss within the first 2 hours was recorded by staff nurse. If delayed excessive hemorrhage occurred, the amount of that was added. Any excessive bleeding with clinically diagnosed uterine atony was treated by other additional uterotonic drugs in accordance with the research protocol, and records were kept. Hemoglobin level was measured between 12 and 48 hours after delivery. Women's vital signs and side effects (nausea, vomiting and headache) were monitored for 6 hours after delivery by nursing staff not involved in the study.

The primary outcome was postpartum blood loss. Secondary outcomes included postpartum hemorrhage, side effects, need for additional uterotonic drugs, need for blood transfusion and change in hemoglobin level after delivery, which is directly associated with blood loss.

SPSS 22 software was used for data analysis after completion of the study enrollment and follow-up. Analysis was done with the help of a computer using Chi-square test, Fisher's exact test, student's T-test and Mann-Whitney U Test. A p-value of < 0.05 was regarded as statistically significant.

Results

During the recruitment period, 340 women were screened for eligibility. Eight women were initially found to be ineligible owing to the presence of previous postpartum hemorrhage (1 woman), severe anemia (1 woman), parity greater than four (1 woman) and pre-eclampsia (5 women). Subsequently, 4 women had cesarean delivery, and 5 women had instrumental delivery resulted in the further exclusion of 9 women.

A total of 323 women were eligible during the study period, and all consented enrolled in the study. Of these, 162 were randomly assigned to the combination of oxytocin and ergometrine group and 161 were randomly assigned to the oxytocin group.

Both groups were comparable in age, gestational age, parity, episiotomy, induction or augmentation of labor, pre-delivery hemoglobin, BMI, duration of labor and birth weight (Table 1). There was no significant difference between oxytocin plus ergometrine group and oxytocin group in postpartum blood loss (145 [100-200] ml versus 150 [100-200] ml, p=0.979) (Table 2). No woman reported PPH in oxytocin plus ergometrine group, compare to 1 woman (0.6%) in oxytocin group (p=0.498). There was no postpartum blood loss of ≥1,000 ml or maternal death. Other secondary outcomes, such as mean postpartum hemoglobin concentration, change in postpartum hemoglobin level, duration of the third stage of labor, use of additional oxytocic drugs, need for blood transfusion and nausea were not different between the two groups. Hypertension wasmore frequently in oxytocin with ergometrine group than oxytocin alone group (6.2% versus 0%, p=0.001).

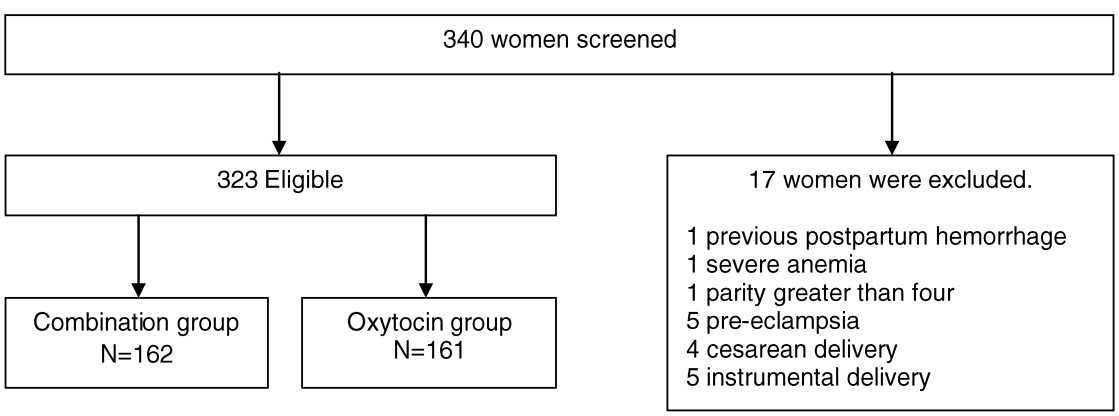

Fig. 1. Flow chart of patients in the study.

Table 1. Demographic and obstetric characteristics of the participants.

	Oxytocin+Ergometrine N = 162	Oxytocin N = 161	P
Age (years)	24.9 ± 6.5	25.0 ± 6.0	0.867*
Gestational age at delivery (weeks)	38.4 ± 1.6	38.4 ± 1.4	0.842*
Parity			0.099†
Primipara	54 (33.3)	68 (42.2)	
Multipara	108 (66.7)	93 (57.8)	
Episiotomy			0.502‡
Yes	161 (99.4)	161 (100)	
No	1 (0.06)	0 (0)	
Induction/Augmentation of labor	35 (21.6)	25 (15.5)	0.160†
Pre-delivery Hemoglobin (g/dl)			0.104†
< 11	32 (19.8)	21 (13)	
≥ 11	130 (80.2)	140 (87)	
BMI, kg/m^2			0.144†
< 18.5	9 (5.5)	3 (1.9)	
18.5 - 24.9	63 (38.9)	58 (36)	
25.0 - 29.9	68 (42.0)	67 (41.6)	
≥ 30	22 (13.6)	33 (20.5)	
Duration of first stage of labor (hours)	7 [5-10]	7 [5-9]	0.674§
Duration of second stage of labor (minutes)	13 [7-25]	14 [8-25]	0.342§
Birthweight (g)	3005.53 ± 379.44	3073.58 ± 355.5	0.097*

Data are presented as mean ± SD or n (%) or median [IQR]

* Student's T-test , † Chi-square test, ‡ Fisher's exact test, § Mann-Whitney U Test

Table 2. Outcome measures of the study.

	Oxytocin+ Ergometrine N = 162	Oxytocin N = 161	P
Postpartum blood loss (ml)	145 [100-200]	150 [100-200]	0.979§
PPH	0	1 (0.6)	0.498‡
Hemoglobin (g/dl) 12–48 hours after delivery	11 [10.1-12]	11.2 [10.2-12.1]	0.251§
Change in Hemoglobin (g/dl)	0.8 [0.4-1.4]	0.9 [0.5-1.5]	0.118§
Duration (minutes) of third stage of labor	5 [3-9]	4 [3-7]	0.196§
Hypertension	10 (6.2)	0	0.001†
Blood Transfusion	2 (1.2)	1 (0.6)	0.502‡
Additional uterotonics	0	2 (1.2)	0.248‡
Nausea	1 (0.6)	2 (1.2)	0.498‡

Data are presented as median [IQR] or n (%)

§ Mann-Whitney U Test, ‡ Fisher's exact test, † Chi-square test

Discussion

Despite marked improvements in the obstetric management, primary PPH remains a significant contributor of maternal morbidity and mortality worldwide. The prophylactic administration of intravenous or intramuscular oxytocin after delivery is the current standard for prevention of PPH[6]. This study revealed no significant differences between both groups in terms of postpartum blood loss, PPH, hemoglobin concentration change, use of additional uterotonics and need for blood transfusion. These findings confirmed the efficacy of intravenous oxytocin in preventing PPH. Additional intravenous ergometrine to oxytocin infusion has no superior effect to oxytocin infusion alone to prevent PPH in vaginal delivery. However, postpartum hypertension was a significant adverse effect in oxytocin plus ergometrine group.

Limitations of this study was the process of delivery which was conducted by various obstetricians causing interpersonal error and blood loss from episiotomy wound.

Studies of other uterotonic agents in preventing PPH are controversy. Systematic reviews, published in the Cochrane Library 2011, on the comparison of ergot alkaloid versus no uterotonic agent concluded that injection of ergot alkaloids in the third stage of labor significantly decreased mean blood loss (mean difference -83.03 ml, 95% CI -99.39 to -66.66 ml), PPH of at least 500 ml (risk ratio (RR) 0.38, 95% CI 0.21 to 0.69) and the use of therapeutic uterotonics (RR 0.25, 95% CI 0.10 to 0.66)[7]. But The Cochrane Library 2013 reported that prophylactic oxytocin was superior to ergot alkaloids in preventing PPH (RR 0.76; 95% CI 0.61 to 0.94) and had fewer side effects, such as hypertension and manual removal of the placenta[6].

Khan et al., and Choy et al. compared oxytocin (10 units) alone with syntometrine (5 units of oxytocin and 0.5 mg ergometrine) in preventing PPH. They found that oxytocin alone was as effective as syntometrine. Median blood loss was similar in both groups. The use of syntometrine was associated with a higher risk of hypertension[9, 10]. In contrast, Yuen et al., reported a 40% reduction of the risk of PPH (OR 0.60, 95% CI 0.21-0.88) and the need for repeated oxytocin injections (OR 0.63, 95%CI 0.44-0.89) in the syntometrine group compared with oxytocin. Side effects, such as nausea, vomiting, headache and hypertension, were uncommon in both groups[11].

Moreover, the Cochrane Library 2009 also reviewed the comparative studies of the PPH prophylaxis by intramuscular syntometrine and oxytocin alone. Syntometrine was more effective than oxytocin alone in the prevention of PPH (OR 0.82, 95% CI 0.71 to 0.95), but not in severe cases. There were significantly more nausea/vomiting and hypertension in the syntometrine group[12]. Nevertheless, report from the Cochrane Library 2013 summarized that there was no benefit seen in the combination of oxytocin and ergometrine versus ergometrine alone in preventing PPH and one study showed evidence that the use of oxytocin and ergometrine was associated with increased mean blood loss (MD 61.0 mL; 95%CI 6.00 to 116.00 mL)[6].

However, these reviews included variability in the doses and preparations of uterotonic agents. It was strongly suggesting only oxytocin 10 IU given as an intravenous bolus. If intravenous administration is not possible, IM administration may be used as this route of administration did show a benefit to prevent PPH greater than 500 mL[6]. There were no conclusive reports of additional second uterotonic agent to oxytocin. We hypothesized that the addition of a second uterotonic agent would be effective in reducing the postpartum blood loss in vaginal delivery. This study evaluates the effect of addition of intravenous ergometrine to a standard oxytocin infusion in Vajira Hospital to reduce blood loss during vaginal delivery. But the results were limited to only low-risk pregnant women. We recommend larger studies and included more general population to confirm these results.

The need to register the trial was not recognized until the study was completed, and thus the trial was retrospectively registered with www.clinicaltrials.in.th. Registration number is TCTR20150820001.

Conclusion

There was no statistically significant difference

in postpartum blood loss during vaginal delivery between oxytocin–ergometrine and oxytocin groups. Hypertension was frequently found in the oxytocin–ergometrine group. However, other adverse effects were not statistically significant differences between both groups.

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การป้องกันภาวะตกเลือดหลังคลอดโดยการให้ยาออกซิโทซิน และ เออร์โกเมทรินร่วมกับออกซิโทซิน ในระยะที่สามของการคลอด

ธิติพันธุ์ น่วมศิริ, เกษมสิษฐ์ แก้วเกียรติคุณ

วัตถุประสงค์: *เพื่อศึกษาเปรียบเทียบปริมาณเลือดที่ออกหลังคลอดในกลุ่มที่ให้ยาออกซิโทซิน และ เออร์โกเมทรินร่วมกับออกซิโทซิน ในหญิงที่คลอดทางช่องคลอด*

วัสดุและวิธีการ: *หญิงตั้งครรภ์จำนวน 323 คน ที่คลอดบุตรทางช่องคลอดที่ภาควิชาสูติศาสตร์-นรีเวชวิทยา คณะแพทยศาสตร์วชิรพยาบาล มหาวิทยาลัยนวมินทราธิราช ถูกคัดเข้าร่วมการศึกษา โดยแบ่งผู้เข้าร่วมการศึกษาออกเป็นกลุ่มที่ได้รับยาออกซิโทซินร่วมกับเออร์โกเมทริน และกลุ่มที่ได้รับยาออกซิโทซินอย่างเดียวหลังคลอดทารก โดยเก็บข้อมูลคือ ปริมาณเลือดที่ออกหลังคลอด ภาวะตกเลือดหลังคลอด ระดับฮีโมโกลบินที่เปลี่ยนแปลง การใช้ยากระตุ้นการหดรัดตัวมดลูก การให้สารประกอบเลือด และผลข้างเคียงอื่นๆ*

ผลการศึกษา: *จากการศึกษาพบว่าปริมาณเลือดที่ออกหลังคลอดไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ ในกลุ่มที่ได้ยาออกซิโทซินร่วมกับเออร์โกเมทริน และกลุ่มที่ได้รับยาออกซิโทซินอย่างเดียว (145 [100] ml versus 150 [100] ml, P=0.979) ไม่มีภาวะตกเลือดหลังคลอดในกลุ่มที่ได้ยาออกซิโทซินร่วมกับเออร์โกเมทริน ในขณะที่กลุ่มที่ได้รับยาออกซิโทซินอย่างเดียวมีภาวะตกเลือดหลังคลอด 1 ราย (0.6%, P=0.498) ระดับฮีโมโกลบินที่เปลี่ยนแปลง การใช้ยากระตุ้นการหดรัดตัวมดลูก การให้สารประกอบเลือดไม่มีความแตกต่างกันในทั้งสองกลุ่ม และพบความดันโลหิตสูงในกลุ่มที่ได้ยาออกซิโทซินร่วมกับเออร์โกเมทริน มากกว่ากลุ่มที่ได้รับยาออกซิโทซินอย่างมีนัยสำคัญทางสถิติ (6.2% Vs 0% p<0.001)*

สรุป: *ไม่พบความแตกต่างกันอย่างมีนัยสำคัญทางสถิติของปริมาณเลือดที่ออกหลังคลอด ระหว่างกลุ่มที่ได้ยาออกซิโทซินร่วมกับเออร์โกเมทริน และกลุ่มที่ได้รับยาออกซิโทซินอย่างเดียว แต่กลุ่มที่ได้ยาออกซิโทซินร่วมกับเออร์โกเมทรินพบความดันโลหิตสูงมากกว่ากลุ่มที่ได้รับยาออกซิโทซินอย่างมีนัยสำคัญทางสถิติ*