วารสารวิชาการสาธารณสุข
ปีที่ 24 ฉบับที่ 2 มีนาคม - เมษายน 2558

Journal of Health Science
Vol. 24 No. 2, March - April 2015

นิพนธ์ต้นฉบับ *Original Article*

A Randomised Controlled Trial of Intravenous versus Intramuscular Oxytocin in the Prevention of Postpartum Hemorrhage during the Third Stage of Labor

Ussanee Sangkomkamhang, M.D.

Athittaya Kruangpatee, M.D.

Department of Obstetrics and Gynecology, Khon Kaen Hospital

Abstract: The objective of this study was to compare the effectiveness of intravenous or intramuscular oxytocin administration in the prevention of postpartum hemorrhage during the third stage of labor. It was conducted as a randomized controlled study among singleton pregnant women underwent vaginal delivery in Khon Kaen Hospital during February – June 2012. The participants were randomly allocated into two groups: group 1 received intravenous oxytocin after delivery of the fetal shoulder and group 2 received intramuscular oxytocin. The primary outcome was the incidence of postpartum hemorrhage, and secondary outcomes were postpartum blood loss, prolonged third stage of labor, additional oxytocin requirement, other additional drugs, blood transfusion, and hypotension during the third stage of labor. Four hundred and fifty pregnant women were enrolled (225 cases in each group). It was found that the incidence of postpartum hemorrhage in intravenous group and intramuscular oxytocin group was 2.2% and 4.8%, respectively. There was no significant difference in the incidence of postpartum hemorrhage (RR 0.45, 95%CI 0.16-1.28). The postpartum blood loss in intravenous oxytocin was significantly lower than that of muscular oxytocin (116.3 ± 6.9 ml vs 154.4 ± 10.5 ml ($p<0.05$)). There was no significant difference in the incidence of prolonged third stage of labor, change in hemoglobin levels 24 hours after delivery, hypotension and blood transfusion in both groups. Additional oxytocin requirement was similar between the two groups. Thus, intravenous oxytocin was associated with lower postpartum hemorrhage and postpartum blood loss when compared to intramuscular oxytocin in the management of the third stage of labor.

Key words: **oxytocin, third stage of labor, postpartum hemorrhage, hypotension**

Introduction

Postpartum hemorrhage (PPH) is a significant cause of maternal morbidity and mortality throughout the world especially in developing countries;[1,2] and uterine atony is the most common etiology.[3] The incidence of postpartum hemorrhage was 3.9% in women delivered vaginally.[4]

Active management in the third stage of labor is the accepted protocol to prevent postpartum hemorrhage. It involves giving a prophylactic uterotonic drug,

controlled cord traction to deliver the placenta and uterine massage. Routine administration of oxytocin has been well established.[4,5] Synthetic oxytocin acts on the smooth muscle of the uterus to stimulate contractions; especially after delivery. When oxytocin binds to oxytocin receptors, it induces intracellular Ca^{2+} releasing and increases prostaglandin secretion, both contribute to the contractile effects leading to the contractions of the uterus.[6] Oxytocin use has been advocated either intramuscularly (10 IU) or as a dilute infusion.[7] Intravenous (IV) bolus has also been used by other authors and they showed that an IV bolus of oxytocin 5 to 10 IU can be used for preventing postpartum hemorrhage after vaginal birth; but it is not recommended in case of elective caesarean section.[7,8]

Some studies reported that rapid bolus injection of oxytocin could result in vasodilatation of arteries and leading to a fall in blood pressure and increase in heart rate.[9] Secher and colleagues studied 9 anaesthetized pregnant women and reported that bolus oxytocin 10 units had resulted in a fall in femoral arterial pressure by 40%, and lowers peripheral and pulmonary resistances by 59% and 44%, respectively within 30 seconds after administration.[8] In contrast, Davies, et al[10] and Foroozanfard, et al[5] found that bolus oxytocin administered during the third stage of labor was not associated with adverse hemodynamic response.

Administration of 10 units of intramuscular oxytocin is routinely recommended for the prophylaxis of PPH in Khon Kaen Hospital. The rate of PPH following vaginal delivery was 3% in 2010. We therefore would like to study a randomized controlled trial to compare the efficacy and safety of intravenous versus intramuscular oxytocin in the management of the third stage of labor. We hypothesized that the intravenous oxytocin could be better than intramuscular administration in preventing PPH. The primary outcome of the study was the incidence of PPH within 24-hour postpartum period and the secondary outcomes were postpartum blood loss, hematocrit level, oxytocin additional dose, other additional drugs, blood transfusion and hypotension during the third stage of labor.

Materials and Methods

The study was conducted in Khon Kaen Hospital during February – June 2012, after approval from the Ethical Committee on Human Research of the hospital. Study samples were singleton pregnant women attending the hospital for vaginal delivery. All women were required to give their written consent at the time of enrolment. Cases with the following conditions were excluded from the study: obstetrics complications, previous history of curettage, previous manual removal of placenta, cardiovascular instability, oxytocin hypersensitivity and medical problems.

The sample size was calculated based on Nordstrom, et al,[11] using 20% as the incidence of PPH with intravenous oxytocin used in the management of the third stage of labour; whereas the incidence of PPH with intramuscular oxytocin was 32% as reported by De Groot, et al.[12] A total sample size of 450 women was calculated to detect the difference with a power of 80% and a Type I error of 0.05.

Four hundred and fifty participants received randomly oxytocin either intravenous or intramuscular technique. The allocation was randomly carried out by using an assignment card placed in a sealed envelope which would be picked by each sample to be assigned into one of the 2 treatment groups: the intra-

venous oxytocin group and the intramuscular oxytocin group. The intravenous oxytocin group (n=225) received intravenously 10 IU of oxytocin diluted in 10 ml of normal saline solution slowly administered over 2 minutes. The intramuscular oxytocin group (n=225) received 10 IU of oxytocin intramuscular injection at maternal deltoid muscle. The injection in both groups was performed after the delivery of fetal anterior shoulder. A baseline (time 0), maternal blood pressure (BP) and heart rate (HR) were recorded between contractions during second stage of labor. After the administration of oxytocin, their BP and HR were measured in accordance with the Khon Kaen Hospital guideline. Postpartum blood loss was measured after cord clamp until complete repaired of episiotomy wound using plastic bags with scale. Also postpartum outcomes such as duration of the third stage of labor, placental retention (>30 minutes), the use of additional uterotonic agents, hematocrit at 24 hours after delivery and blood transfusion were recorded. PPH was observed until 24 hours postpartum periods. Postpartum care was carried out based on the hospital's guideline. Intravenous oxytocin would be immediately terminated if serious complications occurred such as maternal arrhythmias, uncompensated hypotension and water intoxication. Crystalloid solution, inotropic drugs and blood components were prepared to be ready for the treatment of hypotension associated with oxytocin effects; and standard treatment for PPH (uterotonic drugs, bimanual compression and/or surgery) would be given.

Statistical analysis

There were two main parts of analysis: (1) comparison of selected characteristics of the participants and (2) analysis for the study outcomes. For the first part, selected baseline characteristics of the participants in each group were recorded and compared i.e. age, gravidity, parity, gestational age, baseline mean BP and HR, and hematocrit. In this part, percentage was used for summarizing categorical data and mean with standard deviation was used for continuous data.

For the study outcomes, the proportion of the incidence of PPH between two groups was analyzed by using chi-square test and presented with relative risk (RR) with 95% confidence intervals (CI). Postpartum blood loss and change of hematocrit were analyzed by using t-test. The statistical analysis of this clinical trial was performed based on intention to treat principle. Statistical package for all analysis is STATA. A p-value of <0.05 was considered significant.

Results

Altogether 450 singleton pregnant women were recruited into the study at Khon Kaen Hospital during the study period. There was no difference in the demographic characteristics between two groups (Table 1).

The incidence of PPH in intravenous versus intramuscular oxytocin was 2.2% (95%CI 0.01-0.05) and 4.8% (95%CI 0.02-0.08) (p= 0.03), respectively. Intravenous oxytocin was associated with lower rate of PPH when compared to intramuscular oxytocin group, but with no statistically significant difference (RR 0.45, 95%CI 0.16-1.28) (Table 2). Postpartum blood loss in intravenous oxytocin was significantly lower than intramuscular oxytocin (116.3 ± 6.9 ml vs 154.4 ± 10.5 ml (p<0.05)).

The results showed the serial mean arterial pressure (MAP) and mean heart rate (HR) in both groups at 5, and 30 minutes after delivery were not signifi-

cantly difference. At 5 minutes after delivery, MAP in the intravenous group was 87.1 ± 0.5 mmHg and 87.2 ± 0.7 mmHg in the intramuscular group (P=0.91). The mean HR in the intravenous group was 89.1 ± 0.5 and the intramuscular group was 87.9 ± 0.7 beats per minute (p>0.05), respectively (Table 3). There was also no significant difference in the incidence of prolonged third stage of labor (11 cases

Table 1 Demographic data

Characteristics	Intravenous oxytocin (225 cases) (mean ± SD)	Intramuscular oxytocin (225 cases) (mean ± SD)	p-value
Age (years)	24.4 ± 0.4	24.2 ± 0.1	0.68
Gestational age (weeks)	38.6 ± 0.8	38.4 ± 0.1	0.07
parity	0.6 ± 0.1	0.7 ± 0.1	0.19
Mean arterial pressure (mmHg)	89.4 ± 0.5	89.6 ± 0.5	0.78
Baseline pulse rate(bpm)	84.9 ± 0.6	86.5 ± 0.7	0.09
Hematocrit (vol%)	34.6 ± 0.2	34.6 ± 0.2	0.89

Table 2 Incidence of PPH

	Intravenous oxytocin (225 cases)	Intramuscular oxytocin (225 cases)	Relative risk (95% CI)
Postpartum hemorrhage	5	11	0.45 (0.16-1.28)

Table 3 Secondary outcomes

Characteristics	Intravenous oxytocin (225 cases) (mean ± SD)	Intramuscular oxytocin (225 cases) (mean ± SD)	p-value
Postpartum blood loss (ml)	116.3 ± 6.9	154.4 ± 10.5	< 0.01
Mean arterial pressure(mmHg)			
- 5 min	87.1 ± 0.5	87.2 ± 0.7	0.91
- 30 min	88.1 ± 0.5	88.4 ± 0.5	0.62
Heart rate (bpm)			
- 5 min	89.1 ± 0.5	87.9 ± 0.7	0.81
- 30 min	85.1 ± 0.5	82.4 ± 0.5	0.52
Hematocrit at 24 hr postpartum (vol%)	33.7 ± 0.2	33.5 ± 0.2	0.30
Mean difference of hematocrit (vol%)	0.8 ± 0.1	1.1 ± 0.1	0.19

in intramuscular group versus 9 cases in intravenous group), change in hemoglobin levels 24 hours after delivery, hypotension and blood transfusion between the 2 groups. Additional oxytocin requirement was similar between the two groups. There were no serious maternal and fetal complications.

Discussion

This study aimed to determine the incidence of PPH in pregnant women who delivered vaginally. The current study showed no significant difference between intravenous and intramuscular oxytocin in preventing PPH although meaningful reduction was observed (5 cases in the intravenous group, compared to 11 cases in the intramuscular group). However, intravenous oxytocin showed lesser amount of postpartum blood loss. These findings were consistent with the study of Choy, et al which concluded that intravenous oxytocin significantly reduced postpartum blood loss.[13] Some studies reported cardiovascular effects (hypotension, tachycardia) caused by intravenous oxytocin. Conversely, our study found no cardiovascular adverse events which comparable with Foroozanfard, et al[5] and Davies, et al.[10]

Many factors such as variation of health care provider (staff, residents, medical students and nurses), oxytocin infusion before delivery, fetal weight might impact the outcomes. Such factors were manifested equally in the both groups of this study. Therefore these factors had a little effect on the outcomes (data not shown).

An advantage of this study was the power of the methodology – a randomized controlled trial with adequate sample size. Moreover, postpartum blood loss was measured by using measurement blood loss method (plastic bag with scales) which provided more accurate data than the use of estimated blood loss.

Limitation of this study was the characteristic of the samples who were mainly low risk pregnant women of whom the incidence of PPH is usually low. The future study should be conducted in high risk group.

In conclusion, intravenous oxytocin in the management of the third stage of labor should be recommended because there is an evidence of less PPH and postpartum blood loss. In addition, the use of intravenous oxytocin does not increase the risk of adverse events.

Reference

1. Khan K, Wojdyla D, Say L, Gulmezoglu M, Van Look P. WHO analysis of causes of maternal death: A systematic review. Lancet 2006; 367:1066-74.
2. Mbonye AK, Asimwe JB, Kabarangira J, Nanda G, Orinda V. Emergency obstetric care as the priority intervention reduce maternal mortality in Uganda. Int J Gynaecol Obstet 2007;96:220-5.2
3. Bouwmeester FW, Bolte AC, van Geijn HP. Pharmacological and surgical therapy for primary postpartum haemorrhage. Curr Pharm Des 2005;11:759-73.
4. Cunningham FG, Gant NF, Leveno KJ, Gilstrap III LC, HauthJC, Wenstrom KD. Obstetrical hemorrhage. In: Cunningham FG, Gant NF, Leveno KJ, Gilstrap III LC, Hauth JC, Wenstrom KD, editors. Williams's obstetrics. 23rd ed. Columbus (OH): McGraw-Hill; 2010. p. 757-98.
5. Foroozanfard F, Sadat Z, Mousavi GA, Hatami L. Maternal haemodynamic effects of oxytocin bolus or infusion in the third stage of labour. Pak J Med Sci 2011;27:656-9.
6. Viero C, Shibuya I, Kitamura N, Verkhratsky A, Fujihara H, Katoh A, et al. Rewiew: oxytocin: crossing the bridge between basic science and pharmacotherapy. CNS Neurosci Ther 2010;16:e138-56.

7. Priya VR, Wing, Deborah A. Postpartum hemorrhage: evidence- based medical interventions for prevention and treatment. Clin Obstet Gynecol 2010;53:165-81.
8. Secher NJ, Arnsbo P, Wallin L. Haemodynamic effects of oxytocin (syntocinon) and methyl ergometrine (methergin) on the systemic and pulmonary circulations of pregnant women. Acta Obstet Gynecol Scand 1978; 57:97-103.
9. Pinder AJ, Dresner M, Calow C, Shorten G, O'Riordan J, Johnson R. Haemodynamic changes caused by oxytocin during caesarean section under spinal anesthesia. Int J Obstet Anesth 2002;11:156-9.
10. Davies GA, Tessier JL, Woodman MC, Lipson A, Hahn PM. A bolus of oxytocin administered during the third stage of labour was not associated with an adverse hemodynamic response. Evidence-based Obstetrics & Gynecology 2006;8:12-3.
11. Nordstrom L, Fogelstam K, Fridman G, Larsson A, Rydhstroem H. Routine oxytocin in the third stage of labour: a placebo controlled randomised trial. Br J Obstet Gynaecol 1997;104:781-6.
12. De Groot ANJA, Van Roosmalen J, Van Dongen PWJ, Borm GF. A placebo-controlled trial of oral ergometrine to reduce postpartum hemorrhage. Acta Obstet Gynecol Scand1996;75:464-8.
13. Choy CMY, Lau WC, Tam WH, Yuen PM. A randomised controlled trial of intramuscular syntometrine and intravenous oxytocin in the management of the third stage of labour. BJOG 2002;109:173-7.

บทคัดย่อ การเปรียบเทียบผลของออกซิโตซินแบบฉีดเข้าหลอดเลือดดำและฉีดกล้ามเนื้อในระยะที่สามของการคลอด

อุษณีย์ สังคมกำแหง พ.บ.; อาทิตยา เครื่องพาที พ.บ.
กลุ่มงานสูตินรีเวชกรรม โรงพยาบาลขอนแก่น
วารสารวิชาการสาธารณสุข 2558;24:354-9.

การศึกษานี้มีวัตถุประสงคเพื่อเปรียบเทียบผลของออกซิโตซินแบบฉีดเข้าหลอดเลือดดำกับออกซิโตซินแบบฉีดเข้ากล้ามเนื้อในระยะที่สามของการคลอด ใช้วิธีการศึกษาวิจัยแบบสุ่มในสตรีตั้งครรภ์เดี่ยวที่คลอดทางช่องคลอด ในโรงพยาบาลขอนแก่นระหว่างเดือนกุมภาพันธ์ ถึงเดือนมิถุนายน ปี 2555 จำนวนกลุ่มตัวอย่าง 450 คน สุ่มแบ่งเป็นสองกลุ่ม กลุ่มละ 225 คน ซึ่งรับยาฉีดออกซิโตซินเมื่อทารกคลอดไหล่แล้ว โดยกลุ่มหนึ่งได้รับยาเข้าหลอดเลือดดำ และอีกกลุ่มหนึ่งฉีดเข้ากล้ามเนื้อ ผลการศึกษาหลักคืออุบัติการณ์การเกิดการตกเลือดหลังคลอด และผลการศึกษารองได้แก่ ปริมาณเลือดออกหลังคลอด การคลอดที่ยาวนาน การได้รับออกซิโตซินหรือยาอื่น ๆ เพิ่มเติม การรับเลือดและภาวะความดันโลหิตต่ำในระยะที่สามของการคลอด ผลการศึกษาพบว่า อุบัติการณ์การเกิดการตกเลือดหลังคลอดร้อยละ 2.2 และ 4.8 ในกลุ่มฉีดออกซิโตซินเข้าหลอดเลือดดำและฉีดกล้ามเนื้อตามลำดับ โดยไม่มีความแตกต่างทางสถิติอย่างมีนัยสำคัญ (RR 0.45, 95%CI 0.16-1.28) ค่าเฉลี่ยปริมาณเลือดออกหลังคลอดในกลุ่มฉีดกล้ามเนื้อมากกว่ากลุ่มฉีดเข้าหลอดเลือดดำอย่างมีนัยสำคัญ (154.45 ± 10.5 vs 116.33 ± 6.94 มล. ($p<0.05$)) ไม่พบความแตกต่างของการคลอดที่ยาวนาน การลดลงของ hemoglobin ที่ 24 ชั่วโมงหลังคลอด ความดันโลหิตต่ำและการรับเลือดในระหว่างทั้งสองกลุ่ม โดยสรุป การฉีดออกซิโตซินเข้าหลอดเลือดดำในระยะที่สามของการคลอดมีแนวโน้มในการลดการเกิดการตกเลือดหลังคลอดและลดปริมาณเลือดออกหลังคลอดเมื่อเทียบกับการฉีดออกซิโตซินเข้ากล้ามเนื้อ

คำสำคัญ: **ออกซิโตซิน, ระยะที่สามของการคลอด, ภาวะตกเลือดหลังคลอด, ความดันโลหิตต่ำ**