Original Articles/นิพนธ์ต้นฉบับ

Comparison of postpartum blood loss between intravenous carbetocin and intravenous methylergometrine maleate administered immediately at the third stage of labor

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Abstract

Background: Postpartum hemorrhage (PPH) is a major cause of maternal death and is accounted for 25% of maternal deaths worldwide. Nowadays, administration of uterotonic drugs to stimulate uterine contraction can prevent postpartum hemorrhage.

Objective: To compare postpartum blood loss and side effects between use of intravenous carbetocin and intravenous methylergometrine maleate administered immediately after child birth.

Methods: This quasi experimental study applied purposive sampling of 64 parturients. They were divided into 2 groups of 32 cases each who received either intravenous carbetocin or intravenous methylergometrine maleate during the third stage of labor. All parturients were managed during first and second stage of labor in the same way according to the principle of active management of labor. Outcome measures were the postpartum blood loss, duration of third stage of labor, side effects of drug and complications after delivery. Descriptive statistics included percent, mean and standard deviation. Chi-square test, Fisher's exact test and Mann-Whitney U test were applied to test hypothesis with the significant level at $P < 0.05$.

Result: There was no significant difference in demographic characteristics, duration of first, second and third stage of labor and birth weight between the two groups. Rate of PPH, side effect of drugs and complication during delivery were comparable between both groups. But the parturients who received carbetocin intravenously had less mean blood loss, slower pulse rate, lower diastolic blood pressure and lower systolic blood pressure than parturients who received methylergometrine maleate.

Conclusion: Intravenous carbetocin administered immediately after childbirth were more effective than intravenous methylergometrine maleate in prevention of postpartum blood loss among parturients of normal vaginal delivery. There were significantly less mean blood loss, slower pulse rate, lower diastolic blood pressure and lower systolic blood pressure among parturients who received intravenous carbetocin after delivery compared to those who received intravenous methylergometrine maleate. Carbetocin is a more preferable drug in reduction of postpartum blood loss and more safety in side effects of drugs than methylergometrine maleate.

Keywords: Postpartum haemorrhage/ methylergometrine maleate/ carbetocin/ third stage of Labor

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Introduction

Postpartum hemorrhage (PPH) is still the most common cause of maternal mortality and is accounted for 25% of the maternal death worldwide[1]. Uterine atony is a major cause of PPH by 67-80%[2]. In Thailand postpartum hemorrhage was the major leading cause of maternal mortality estimated to be 20-45 % of maternal mortality.

World Health Organization has recommended that all women giving birth should be offered uterotonics during the third stage of labour for the prevention of PPH. Oxytocin 10 units, IM/IV, was recommended as the uterotonic drug of choice[3].

In Ramathibodi Hospital, the protocol of active management of labor has been established since 1976. Intravenous administration of methylergometrine maleate immediately after anterior shoulder birth as an active management of third stage of labor was routinely applied. This protocol has been working till today but methylergometrine maleate has limitation about half-life for stimulated the contraction shorter than carbetocin(oxytocin analogue) and the side effects of methylergometrine maleate as nausea, vomiting and elevated blood pressure were more aware of and monitored.

Carbetocin is a new drug that begin to use for prevention postpartum haemorrhage in parturient. Because carbetocin is a new long acting synthetic analogue of oxytocin, with a half-life of approximately 4-10 times longer than oxytocin. Rhythmic uterine contractions persist for 60-120 minutes after intravenous and intramuscular injection, respectively. Carbetocin can be administered as a single dose injection, whereas oxytocin requires repeated injections or a perfusion of several hours. Carbetocin is proposed to be more effective in prevention and treatment of PPH than oxytocin[2].

The objective of this study was to compare postpartum blood loss, duration of labor, complication of delivery and side effects of drugs between the use of intravenous carbetocin(oxytocin analogue) and methylergometrine maleate as an active management of the third stage of labor.

Methods

This quasi-experiment study was carried out during 1st March 2014 and 31st May 2014 at delivery room, Ramathibodi Hospital, Bangkok, Thailand. Approval for the study was obtained from the Committee on Human Rights Related to Research Involving Human Subjects, Faculty of Medicine Ramathibodi Hospital, Mahidol University (MURA2013/642). Parturients who had cervix opened more than 6 centimeters was exclude from this study. Sixty four parturients who had normal vaginal delivery were recruited by purposive sampling and sample allocation. They were divided nullipara parturients into 2 groups of 32 cases to decrease bias about postpartum haemorrhage in multipara parturients. Carbetocin group (n=32) were parturients who received intravenous carbetocin and methylergometrine maleate group (n=32) were parturients who received intravenous methylergometrine maleate.

The inclusion criteria of parturients were parturients who were nullipara, aged 18-30 years old with singleton pregnancy. They were without complication during antenatal care such as hypertension during pregnancy and had normal vaginal delivery with repair episiotomy wound. They were excluded from study if they had to caesarean section, had history of drug allergy to oxytocin, carbetocin and methylergometrine maleate or they refused to participate during the study.

After anterior shoulder birth of the baby, parturients who were allocated into the carbetocin group received intravenous carbetocin 0.1 mg and

those who were in methylergometrine maleate group received intravenous methylergometrine maleate (Methergin®) 0.2 mg. Both drugs were not blinded for nurses who gave the injection.

In both groups, protocol of active management of third stage of labor was applied which included controlled cord traction for delivery placenta and uterine massage after delivery of placenta.

Postpartum blood loss was measured from the beginning of third stage of labor (after the birth of newborn) till 2 hours after delivery (Acute postpartum hemorrhage). Plastic pad was used to collect blood and was put under parturient's hip. All plastic pad, swab and gauzes used to absorb blood were collected, weighted and calculated for amount of blood loss.

The SPSS software package version 18 licensed from Mahidol University was used for data analysis. Chi-square test, Fisher's exact test and Mann-Whitney U test were used to test hypothesis with the significant level at $P<0.05$.

Results

Characteristics of parturients in both groups are not statistically significantly different. Mean ages were 25.2±4.12 years in carbetocin group and 24.7±3.9 years in methylergometrine maleate group. Their mean weights were 67.3±10.9, and 63.9±10.7 respectively. Mean height were 160.1±4.7, and 160.4±5.5 respectively. They delivered their babies at 38 wks of gestational age with mean birth weight 2976.6±257.1 in carbetocin group and 2951.6±275.5 grams in methylergometrine maleate group. (Table 1).

Table 2 shows mean postpartum blood loss were less in carbetocin group compared to methylergometrine maleate group. The mean postpartum blood loss by measurement in carbetocin group were 246.91 ml (SD=67.32) and methylergometrine maleate group were 312.53 ml (SD=153.44) respectively. There were significant difference between two groups (P=0.038). The duration of labor were comparable in every stage of labor as well as duration of labor augmentation. The difference was statistically significant ($P<0.05$). (Table 2).

Table 3 showed that there were 2 cases (6.25%) of nausea and vomiting in methylergometrine maleate group but none in carbetocin group. There was no significant difference between the two groups.

Table 1 Characteristics of the parturients

Characteristics	Carbetocin N=32 (SD)	MM N=32 (SD)	χ^2	P-value
Age (years)	25.2 (4.12)	24.7 (3.9)	0.14	0.93
Height (cms.)	160.1 (4.7)	160.4 (5.5)	0.10	0.75
Weight (kgs.)	67.3 (10.9)	63.9 (10.7)	1.59	0.21
Total weight gain (kgs.)	13.9 (4.4)	12.2 (3.1)	0.00	1.00
Gestational age (wks.)	38.8 (1.0)	38.6 (1.2)	0.06	0.80
Birth weight (gms.)	2976.6 (257.1)	2951.6 (275.5)	0.57	0.45

MM = Methylergometrine maleate, 1 = Fisher's exact test

Table 2 Postpartum blood loss, duration of labour

Characteristics	Carbetocin N=32 (SD)	MM N=32 (SD)	χ^2	P-value
Duration of labor augmentation (mins.)	111.1 (86.9)	121.3 (134.4)	0.35	0.56
Duration of first stage of labor (mins.)	608.9 (147.8)	490.3 (162.0)	1.82	0.18
Duration of second stage of labor (mins.)	17.6 (12.4)	15.9 (9.7)		1.00[1]
Duration of third stage of labor (mins.)	3.5 (2.2)	3.9 (1.9)		0.13[2]
Postpartum blood loss (mls.)	246.9 (67.3)	312.5 (153.4)		0.03[2]

MM = Methylergometrine maleate, 1 = Fisher's exact test, 2 = Mann-whitney U test

Table 3 Side effect of drugs.

Characteristics	Carbetocin No. (%) n=32 (100)	MM* No. (%) n=32 (100)	Fisher's Exact Test	df	p - value
Nausea and vomitting	0 (0.00)	2 (6.25)			0.47

*MM = Methylergometrine maleate

Discussion

Carbetocin is a synthetic analogue of oxytocin with a half-life of approximately 4-10 times longer than oxytocin. Carbetocin can be administered as a single dose injection either intravenously or intramuscularly compared with oxytocin which is administered by infusion over several hours[2].

Our study showed that the mean volume of postpartum blood loss among parturients receiving intraveneous carbetocin was significantly less than those receiving intraveneous methylergometrine maleate. This study was in accordance with the others[4,5]. In 2008, Ngan L. and associates compared parturients who received either a single 100 μg dose of carbetocin or a combination of 5 IU oxytocin and 0.2 mg ergometrine (Syntometrine®) administered intravenously after vaginal delivery. Their results showed that mean blood loss after carbetocin administration was less than that after Syntometrine® (P<0.01). The incidence of postpartum hemorrhage was significantly reduced in the carbetocin group (P <0.01)[4]. Also in 2008, Nirmala K. and associates studied 120 pregnant women who delivered vaginally. They were randomized into two groups, i.e., the study group who received 100 μg intramuscular carbetocin and the control group who received intramuscular Syntometrine®. There was a significantly lower mean estimated blood loss in the carbetocin group compared to the Syntometrine® group[5].

The clinical and pharmacological properties of carbetocin are similar to those of natural oxytocin which is another posterior pituitary hormone. The onset of uterine contraction following carbetocin administration by either the intravenous or intramuscular route is rapid, with a firm contraction being obtained within 2 minutes.

Rhythmic uterine contractions persist for 60 and 120 min after intravenous and intramuscular injection, respectively. The side effect of carbetocin was similar as oxytocin. Intravenous carbetocin is frequently associated with nausea, abdominal pain, pruritis, flushing, vomiting, feeling of warmth, hypotension, headache and tremor[2].

Methylergometrine maleate is an ergot alkaloid with similar action on myometrium. Whether given intravenously, intramuscularly or orally, ergot alkaloids are powerful stimulants of myometrial contraction, exerting an effect that may persist for hours and rapidly stimulate tetanic uterine contractions and act for approximately 45 minutes. They also act on other smooth muscle and cause vasoconstriction. When the drug is given intravenously, dangerous hypertension may occur, especially in women with preeclampsia, or existing hypertension[6].

Most of the drugs used during delivery have effects on cardiovascular status of mothers and should be aware of. In this study mean average of pulse rate after placenta delivery in carbetocin group decreased significantly more than in methylergometrine maleate group (P <0.05). Diastolic blood pressure (DBP) also decreased more in carbetocin group than in intraveneous methylergometrine maleate group with a significant difference at 60 minutes after placental delivery. Systolic blood pressure (SBP) significantly increased less in carbetocin group than in methylergometrine maleate group with a significant difference at 30 minutes after placenta delivery (P <0.05).

These findings were also in accordance with the study of Moertl and associates who studied the effect on maternal heart rate of carbetocin 100 μg or oxytocin 5 IU during elective caesarean section in 56 parturients. They found that maternal heart rate decreased in carbetocin group more than in oxytocin group. In addition, systolic blood pressure decreased in carbetocin group more than oxytocin group[7].

In this study there were 2 cases (6.25%) of nausea and vomiting in methylergometrine maleate group but none in carbetocin group. This study also found complication of delivery only in the methylergometrine maleate group. There was one case who needed more uterotonic drug in methylergometrine maleate group.

The study of Su and associates found neither significant difference in postpartum hemorrhage nor need of use of more uterotonic drug between parturients who received carbetocin 100 μg compared to those who received Syntometrine®. They found only 1.6% of postpartum hemorrhage. But 13% of parturients in carbetocin group needed additional uterotonic drugs compared with 16.8% in the Syntometrine® group. However, the difference was not statistically significant[8].

This study could not apply a double blind and systemic randomization strategy because of the irregular supply of carbetocin. The drug was supplied in lot for a period of time and the number of parturients during the study period was not matched with the supply. Time of study was also limited. Some differences in this study were also not significant due to small sample size. However, the main object of this study was to measure blood loss after delivery which showed a significant difference.

In conclusion, intravenous carbetocin was more effective than intravenous methylergometrine maleate in the prevention of postpartum blood loss among parturients of normal vaginal delivery with significantly less mean blood loss. Carbetocin group also had significant slower pulse rate, lower diastolic blood pressure and lower systolic blood pressure than methylergometrine maleate group.

Side effects and complication were found only in methylergometrine maleate group. Carbetocin is a more preferable drug in reduction of postpartum blood loss and more safety in side effects of drugs than methylergometrine maleate.

Conflict of interest

For the study Carbetocin (Duratocin®) was supplied by Ferring Pharmaceuticals Limited.

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Original Articles/นิพนธ์ต้นฉบับ

เปรียบเทียบปริมาณการเสียเลือดหลังคลอดระหว่างการได้รับยา CARBETOCIN และยา METHYLERGOMETRINE MALEATE ทางหลอดเลือดดำในระยะที่สามของการคลอด

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บทคัดย่อ

ความเป็นมา: ภาวะตกเลือดหลังคลอด เป็นสาเหตุอันดับหนึ่งของการเสียชีวิตของมารดา พบถึงร้อยละ 25 ของสาเหตุการเสียชีวิตของมารดาทั่วโลก ปัจจุบันมีการให้ยากระตุ้นการหดรัดตัวของมดลูก สามารถช่วยป้องกันการตกเลือดหลังคลอดได้

วัตถุประสงค์: เพื่อเปรียบเทียบปริมาณการเสียเลือดหลังคลอดและภาวะแทรกซ้อนในสตรีผู้คลอดระหว่างการได้รับยา carbetocin และยา methylergometrine maleate ทางหลอดเลือดดำทันทีหลังคลอดในสตรีที่คลอดบุตรปกติทางช่องคลอดปกติ

วิธีวิจัย: การวิจัยนี้เป็นแบบกึ่งทดลอง โดยเลือกกลุ่มตัวอย่างแบบเฉพาะเจาะจงทั้งหมด 64 ราย แบ่งเป็น 2 กลุ่มๆละ 32 ราย คือกลุ่มได้รับยา carbetocin ทางหลอดเลือดดำและกลุ่มได้รับยา methylergometrine maleate ทางหลอดเลือดดำในระยะที่สามของการคลอด การดูแลการคลอดในระยะที่หนึ่งและระยะที่สองของการคลอด ตามหลักการดูแลการคลอดแบบตื่นตัวเหมือนกันทั้งสองกลุ่ม เก็บข้อมูล ผลการคลอดและการเสียเลือด ระยะเวลาระยะที่สามของการคลอด ภาวะแทรกซ้อนของการคลอดและภาวะแทรกซ้อนของยา สถิติเชิงพรรณาใช้จำนวน ร้อยละ ค่าเฉลี่ย ส่วนเบี่ยงเบนมาตรฐาน และใช้ Chi squaretest, Fisher's exact test และ Mann-Whitney U test ในการทดสอบสมมติฐาน โดยให้ระดับนัยสำคัญที่ $P = 0.05$

ผลการศึกษา: กลุ่มได้รับยา carbetocin และกลุ่มได้รับยา methylergometrine maleate มีลักษณะทั่วไประยะเวลาของการคลอดรวมถึงน้ำหนักทารกแรกเกิดไม่แตกต่างกัน พบว่าอัตราการตกเลือด อาการข้างเคียงและภาวะแทรกซ้อนในการคลอดและหลังคลอดไม่แตกต่างกัน แต่พบว่ากลุ่มที่ได้ยา carbetocin เสียเลือดน้อยกว่าและมีการลดลงของชีพจร ความดันโลหิตไดแอสโทลิคและซิสโทลิค ลดลงมากกว่ากลุ่มที่ได้ยา methylergometrine maleate อย่างมีนัยสำคัญทางสถิติ

สรุป: การใช้ยา carbetocin ฉีดเข้าทางหลอดเลือดดำหลังคลอดทันทีในสตรีที่คลอดปกติทางช่องคลอด มีประสิทธิผลดีกว่าการใช้ยา methylergometrine maleate ทำให้ปริมาณการเสียเลือดหลังคลอดน้อยกว่า ชีพจรช้าลง ความดันโลหิตไดแอสโทลิคและซิสโทลิคลดลง มากกว่ากลุ่มที่ใช้ยา methylergometrine maleate อย่างมีนัยสำคัญทางสถิติ ทำให้ยา carbetocin เป็นยาที่เหมาะสมกว่ายา methylergometrine maleate ในการป้องกันการเสียเลือดหลังคลอดและมีความปลอดภัยจากภาวะแทรกซ้อนของยามากกว่า

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