CARBETOCIN VERSUS SYNTOMETRINE IN THE PREVENTION OF POSTPARTUM HAEMORRHAGE AMONG WOMEN WITH RISK FACTOR FOLLOWING VAGINAL DELIVERY

BY

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ABSTRACT

Postpartum haemorrhage (PPH) is one of the main factors that contribute to maternal morbidity and mortality worldwide. The aim of this study was to compare the efficacy and safety of a single 100μg intramuscular (IM) dose of carbetocin to a single IM dose of syntometrine in the prevention of PPH for patient with at least one risk factor for PPH following vaginal delivery. This study was a double blind randomized controlled study conducted in tertiary centre whereby 140 pregnant women with risk factors of PPH who delivered vaginally. 70 of pregnant women received IM syntometrine and another 70 women received IM carbetocin during third stage of labour. All outcomes measure including, the amount of intrapartum blood loss, haemoglobin differences between pre and 24 hours post-delivery, additional uterotonic agents requirement and drugs side effects were evaluated. All the data were analysed using chi-square test and independent t-test. The amount of intrapartum blood loss was significantly lower in carbetocin group compared to syntometrine group (304.43 ± 192 vs 402.19 ± 265). Besides, the number of women needed additional uterotonic agents was also higher in syntometrine group compared to carbetocin group. 15 women out of 70 needed additional uterotonic agents in syntometrine group compared to 5 women in carbetocin group and it was statistically significant (15/70 vs 5/70, p value < 0.016). The number of women developed PPH (EBL more than 500mL) was also higher in syntometrine group compared to carbetocin group and it was statistically significant (22.9% vs 10%, p value 0.04). However, there was no significant difference regarding the incidence of major PPH, blood transfusion requirement and haemoglobin differences. There were also lower incidence of drug side effects in carbetocin group compared to syntometrine group (5/70 vs. 23/70). This study showed that IM carbetocin is more effective in reducing the intrapartum blood loss. Thus it is benefit in prevention of PPH among high-risk pregnant women who delivered vaginally.

APPROVAL PAGE

I certify that I have supervised and read this study and that in my opinion, it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Master of Obstetrics and Gynaecology.

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PPH	Postpartum haemorrhage
IM	Intramuscular
Hb	Haemoglobin

CHAPTER ONE

INTRODUCTION

Postpartum haemorrhage (PPH) is one of the major problems that contribute to maternal morbidity and mortality worldwide. Definition of Primary PPH is blood loss from genital tract more than 500mL that occur within 24 hours. It can be classified as minor (500 – 1000mL) or major if the blood loss is more than 1000mL (Royal College of Obstetricians and Gynaecologists [RCOG], 2011).

Primary PPH was the third highest direct cause of maternal death based on Maternal Death 2003 – 2005 report adapted from UK Confidential Enquiry (RCOG, 2011). Comparable in Malaysia, primary PPH is considered as top three important causes of maternal deaths (Yadav, 2012) . Maternal Death report in Malaysia (2001 – 2005) showed that incidence of PPH was 13.6 % of 125 maternal deaths and most of them were due to uterine atony followed by retained products of conception (Siva Achanna, 2011). Death from PPH is highly preventable. It is essential that first-line midwives and doctors are able to prevent, make early detection and prompt management of primary PPH. Hence it is important to focus on aggressive measures in reducing the incidence of PPH as well as maternal deaths in Malaysia.

Since its effect in maternal morbidity and mortality worldwide, it is important to actively manage women during the third stage of labour in order to reduce risk of PPH. Several studies have proven that by the use of prophylactic uterotonic agents, it can decrease cases of PPH by 60% (RCOG, 2011).

Mechanism of action of syntometrine is by combination of the sustained oxytocic action of 0.5mg ergometrine with rapid action of 5IU oxytocin on the uterus given intramuscularly after delivery of the baby's anterior shoulder. It is the first line

drug of choice used in the Labour Room Hospital Tengku Ampuan Afzan Kuantan except for those who had hypertensive disorder or known to have heart disease. Carbetocin is effective to prevent atonic uterus. It is a long-acting synthetic analogue of oxytocin with half-life of up to 4 to 10 times longer than that of oxytocin. It is a single-dose IM injection and is more effective in prevention of PPH and lesser side effects based on several international studies (Askar, Ismail, El-Ezz, & Rabie, 2011; Su, Chong, & Samuel, 2012; Samimi, Imani-Harsini, & Abedzadeh-Kalahroudi, 2013).

Although active management of third stage of labour have been practised worldwide using oxytocin, PPH still remains one of the important factor of maternal mortality elsewhere. Carbetocin is a new drug and the efficacy of this drug had been proven in caesarean section but lack of data and research in cases of vaginal delivery. Studies were mainly focused in low risk patients without risk factors for PPH. There was one local study which was done in UKM focused on high risk patients delivered vaginally, however, in this study there was no exclusion for confounding factors such as episiotomy or genital tract trauma which may contribute in intrapartum blood loss (Nirmala, Zainuddin, & Ghani, 2009). Therefore, this study is to compare the efficacy between carbetocin and syntometrine group in prevention of atonic uterus that lead to PPH among high risk women delivered vaginally after excluding confounding factors, which may help us to have more evidence for the efficacy of carbetocin in the prevention of PPH. This clinical trial is by intention to treat as every woman who delivered vaginally will be given prophylactic uterotonic agent.

Several randomized trials have compared syntometrine with carbetocin among women who delivered vaginally. These trials have found that carbetocin is better and effective in prevention of PPH among women without risk factor (Askar et al., 2011;

Samimi et al., 2013), but in other studies, they found that there weren't any significant difference in efficacy between these two drugs (Leung, Ng, Wong, & Cheung, 2006; Su et al., 2009). Among women with high risk factor of PPH, few trials revealed that carbetocin appeared to be at least as effective as other conventional regime and carbetocin is not recommended as routine used in view of the cost (Boucher et al., 2004; RCOG, 2011). However, few study revealed that carbetocin is effective as prophylaxis of PPH among women with risk factor (Maged, Hassan, & Shehata, 2016; Nirmala et al., 2009). There is no meta-analysis comparing carbetocin and syntometrine for vaginal delivery.

Based on the knowledge and literature review, there are only few published studies comparing the efficacy of syntometrine and carbetocin in high risk women who delivered vaginally. In view of conflicting data regarding the efficacy of carbetocin, this study was designed to compare the efficacy as well as safety of a single 100µg IM dose of carbetocin to a single IM dose of syntometrine in the prevention of primary PPH in women with at least one risk factor for PPH after successful vaginal delivery. The specific objectives of this study were:

1) To measure the amount of intrapartum blood loss
2) Requirement of additional uterotonic agents
3) Need of blood transfusion
4) Haemoglobin differences pre & post-delivery
5) Side effects of both drugs.

CHAPTER TWO

LITERATURE REVIEW

PPH is caused by four elements generally which are tone, trauma, tissue and thrombin. However, uterine atony contributes to 67 – 80 % of cases that cause PPH (Rath, 2009). All women who delivered vaginally should offered prophylactic uterotonic agent as it can reduce the risk of PPH by 60%. According to literature, there was no identifiable risk factors in most cases of PPH (RCOG, 2011). Carbetocin is a potent and long-acting uterotonic agent that produced sustained uterine contraction within 2 minutes compared to Syntometrine that produced uterine respond within 2-7 minutes.

There was study done among high risk women showed that, syntometrine group bled 100mL more higher compared to carbetocin group and the difference in the mean estimated blood loss was significant (Nirmala et al., 2009). In women with no risk factor, trials showed that, there was no significant difference demonstrated between the carbetocin group and syntometrine group in terms of estimated mean blood loss and the used of additional uterotonic agents (Su et al., 2012).

Local study done in University of Kebangsaan Malaysia in the Obstetrics and Gynaecology Department, among pregnant lady with at least one risk factor of PPH, they found that carbetocin had significantly lower mean estimated blood loss compared to the syntometrine group (244mL ± 114 mL vs 343 ± 143 mL). Drop in haemoglobin level was also reduced significantly in carbetocin group compared to the syntometrine group (0.3 ± 0.2 g/dL vs 0.4 ± 0.2 g/dL) (Nirmala et al., 2009). Other trials compared carbetocin with syntometrine for women undergoing vaginal deliveries in low risk group, two of these trials showed that the estimated blood loss

during the third stage of labour was similar between the two groups (p = 0.294) (Askar et al., 2011). However, another two trials conducted in Hospital TAIBA Kuwait and Shabikhani Maternity Centre Iran revealed that, there was a statistically highly significant difference in the estimated mean blood loss between carbetocin and syntometrine groups, with a blood loss of 81.5 mL higher in syntometrine group (Samimi et al., 2013).

In terms of haemoglobin differences, there were few trials done among low risk and high risk women who delivered vaginally showed that there was a significantly reduced drop in haemoglobin in the carbetocin compared to the syntometrine group (Askar et al., 2011; Nirmala et al., 2009; Samimi et al., 2013). Based on local study done in HUKM among the high risk women, syntometrine group showed significant drop in haemoglobin with a mean difference of 0.2 g/dL as compared to the carbetocin group (Nirmala et al., 2009).

Other than that, regarding the usage of additional uterotonic agents, one study revealed that there were significant differences between carbetocin and syntometrine group among women in low-risk group of PPH (p=0.002) (Samimi et al., 2013). In other study done among high risk mother, they found that, carbetocin group showed less requirement for the need of additional uterotonics agent compared to syntometrine group (Maged et al., 2016).

Based on prospective double-blind randomised controlled trial done among pregnant lady without risk factor of PPH, they found that women who had syntometrine were four times more likely to experience nausea and vomiting compared with women received carbetocin. Tremor, sweating and uterine pain were also more likely in the syntometrine group compared with the carbetocin group ($p < 0.05$) (Askar et al., 2011). However, in other study done among mother with high risk

group of PPH, there was no significant difference between 2 groups in the occurrence of nausea, vomiting, tachycardia, dizziness, palpitation and itching (Maged et al., 2016). A study assessing the uterotonic effects of various doses of IM carbetocin on postpartum uterus following vaginal delivery showed that those women with carbetocin experienced abdominal cramping (Hunter, Schulz, & Wassenaar, 1992).

CHAPTER THREE

METHODOLOGY

This prospective randomized, double blind clinical trial were organized and carried out in the High Risk Labour Room of Hospital Tengku Ampuan Afzan Kuantan. This clinical trial was approved by the Clinical Research Centre of the Hospital Tengku Ampuan Afzan as well as Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia (MOH) NMRR-16-2075-33150 (IIR).

All pregnant women with at least 1 risk factor of PPH age above 18 years old beyond 36 weeks of gestation with a viable fetus successfully delivered vaginally participated in this study. 175 pregnant women who agreed and gave informed consent involved in this study and randomly been divided into syntometrine or carbetocin group respectively.

3.1 INCLUSION AND EXCLUSION CRITERIA

Based on a review of acknowledged resources, we identified several risk factors of PPH and included in the inclusion criteria (Al-Zirqi, Vangen, Forsen, & Stray-Pedersen, 2008; Bais, Eskes, Pel, Bonsel, & Bleker, 2004; Stones, Paterson, & Saunders, 1993). The risk factors that included in this study were a history of PPH in previous pregnancy, history of retained placenta, grandmultipara (para 5 and above), multiple pregnancy, fetal macrosomia (clinical EFW 3.8 – 4 kg and confirm post-delivery), polyhydromnions (more than Amniotic Fluid pocket > 8cm or AFI > 25cm), augmentation of labour with oxytocin for at least 4 hours, prolong of labour 1st stage

or 2nd stage of labour (more than 12 hours), anemia in pregnancy (Hb less than 9 gm/dL) and maternal obesity (BMI more than 35 kg/m2).

The exclusion criteria for this study were women younger than 18 years old, women with heart disease (previous and current pregnancy), women with hypertension (current pregnancy), past history of hypersensitivity to oxytocin or carbetocin, present of coagulation defect (current pregnancy) and genital tract trauma (second degree tear or more included episiotomy) during current delivery. Women that end up with instrumental delivery or emergency lower segment caesarean section were also been excluded in this study.

Finally, a total of 70 pregnant women in carbetocin group and 70 pregnant women in syntometrine group were recruited in this study.

3.2 STUDY PROTOCOL

Every woman who suitable and followed the above criteria was counselled about the study and informed consent taken during admission to antenatal ward or labour room. They were informed regarding the goals, methods, benefits and possible risks of the study. During admission to labour room, all high risk pregnant women were randomised to receive either IM carbetocin or IM syntometrine. The drugs were labelled with computer-generated randomised code and sealed, consecutively numbered in black medicine sheet before recruitment.

At entry of the labour room, the consent of the subjects to participate in the study was reconfirmed. Baseline blood pressure (BP) and pulse rate (PR) was taken upon admission to labour room. Approximately 4 mls of blood taken for haemoglobin

level 2 times during admission to labour room and repeat 24 hours post-delivery. All medications are permitted during the trial as it is not interfere with this study.

Midwives who were not involved in managing the women will prepare the uterotonic drug. Once the women is about to deliver vaginally, an independent midwife will open the medicine sheet and draw up the study drug. Either IM carbetocin or syntometrine was given by this independent midwife. The women, the nurses and the doctors attending the delivery were blinded to the type of medication that will be injected. Both drugs were kept in the delivery room. The medication codes were only made known after completion of the trial.

Women in carbetocin group received one ampoule of carbetocin (100µg, 1 ml ampoule) and syntometrine group received one ampule (1ml) of syntometrine (5IU of oxytocin and 0.5 mg of ergometrine) intramuscularly soon after delivery of the baby. Blood loss measured immediately after delivery of placenta, where a thick plastic sheet been placed under the patients' thigh and a container below the delivery bed in order to minimize the error of including amniotic fluid and blood absorbed into drapes. All the tampons, gauzes and pads were collected and measured by digital weighing scale. A 100 gram increase in weight was equivalent to 100 mL of blood. Apart from that, few midwifes were recruited and trained in this study to conduct the delivery in order to minimize the error of estimating blood loss.

The third stage of labour been managed as usual by cord clamping and cutting umbilical cord, waiting for signs of placental separation and delivering the placenta by controlled cord traction. Administration of IM carbetocin is only given once as recommended. Therefore, in case of persistant uterine atony during third stage of labour, additional doses of uterotonic agent were given either IM syntometrine, IM Haemabate or IV oxytocin been prescribed by attending doctor. Those women with

massive PPH were actively managed according to the hospital protocols of massive PPH such as insertion of Bakri balloon, internal iliac artery ligation, B-Lynch Suture or hysterectomy.

Following delivery, the vital signs and uterine tone of women were monitored as per routine protocol. Women that required blood transfusion within 24 hours post-delivery will be recorded. Side effects of each drug been administered within first 24 hours post-delivery were documented in the proforma form. Any woman who developed allergic reaction towards drug that had been administered within 24 hours, immediate action and appropriate measured were taken as per hospital protocols according to drug reaction protocols.

The hospital protocols practised routine prophylactic uterotonics agent either delivered vaginally or by caesarean section. Women who developed side effects such nausea, vomiting, headache and abdominal pain were managed accordingly with appropriate medication. Fortunately, based on study research, adverse drug reaction is very rare in both drugs (Rath, 2009).

Participation of the eligible women in this study was 48 hours after delivery as the side effects commonly occurred within this period. All the adverse reaction or side effects that occurred will be informed immediately to the principle investigator in order to reassess and manage accordingly. In case of women who developed adverse events related to drug administered, they were given follow-up until 48 hours post-delivery and appointment to postnatal clinics two weeks upon discharge.

All the data including demographic data, medical history, antenatal history as well as intrapartum events were recorded in the study proforma**.** Assessment of both the efficacy and side effects of the drug was performed in the delivery suite and subsequently in the postnatal ward.

3.3 DATA ANALYSIS

The estimated blood loss (EBL), additional uterotonic agents needed, the Hb differences and the drug side effects were analysed using IBM SPSS version 20. Results were described as mean ± standard deviation (±SD), or frequencies (number of cases) and percentages accordingly. Independent t-test was used to compare the numerical variables between the study groups. For comparing categorical data Chi-square (X^2) test were used. P value of less than 0.05 (p value < 0.05) was considered as statistically significant. The null hypothesis for this study is carbetocin and syntometrine is equally effective in prevention of postpartum haemorrhage among women with risk factors of PPH.

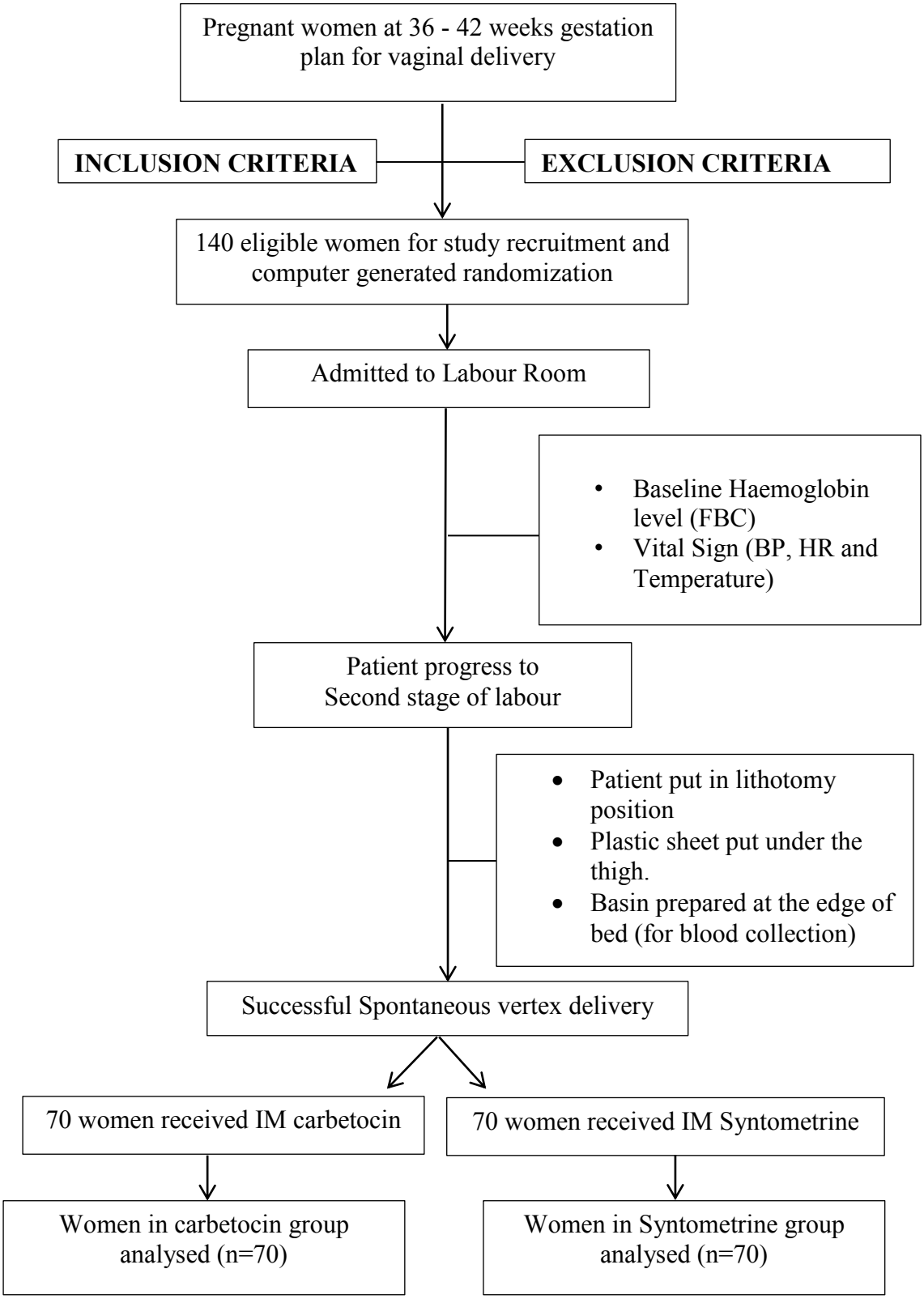

Figure 3.1 Flow chart of patient recruitment

CHAPTER FOUR

RESULT

As in the flowchart Figure 3.1, it showed that 140 pregnant women recruited in this study from January 2017 until January 2018. All women with at least one risk factor of PPH were eligible in this study. If any of the recruited women ended up with instrumental delivery, caesarean section or second-degree and above perineal trauma, the sample of the drug will be substituted with another eligible women that successfully delivered vaginally. Women without risk factor, they were recruited as well if they required pitocin augmentation more than four hours during intrapartum or prolong labour. Finally, 70 women were randomized to receive IM carbetocin and 70 women were randomized to receive IM syntometrine. Informed consent was obtained from all the women before randomisation.

Baseline characteristics between the two randomised groups were similar (Table 4.1). Patient's age range from 19-45 years and mean age for syntometrine and carbetocin group was also similar (33.61±5.91 vs 33.99±5.45). Number of women with para five or more was also similar in each group. Each group was comparable for gestational age at delivery, mean birthweight as well as type of perineal tear. Table 4.2 showed the risk factor of PPH among both groups. There were no significant differences observed between the carbetocin and syntometrine groups in relation to number of individual risk factors.

In this study population, most women had one risk factor of PPH, 45 (64.3%) in syntometrine group and 41 (58.6%) in carbetocin group. Women who developed severe PPH in this study were either had only one risk factor or two risk factors of

PPH. None of the women with multiple risk factors developed severe PPH. However, analysis between number of risk factors and incidence of PPH in this study were not significant (Table 4.3).

Table 4.1 Demographic data

Characteristics	Syntometrine (n=70)	Carbetocin (n=70)	P value
Maternal Age (years) (mean ±SD)	33.61± (5.91)	33.99 (5.45)	0.70
Gestational Age at delivery (weeks), (mean ±SD)	38.14 (1.48)	38.13 (1.25)	0.95
Parity, *n* (%) Primigravida Multipara Grandmultipara	 4 (40%) 31 (52.5%) 35 (49.3%)	 6 (60%) 28 (47.5%) 36 (50.7%)	 0.75
Birth weight (kg), Mean (SD)	3.03 (0.42)	3.04 (0.49)	0.862
Perineal Tear, *n* (%) Intact Mucosal tear First degree tear	 37 (52.8%) 10 (14.2%) 23 (32.8%)	 43 (61.4%) 10 (14.2%) 17 (24.2%)	 0.50 0.50 0.50

Table 4.2 Distribution of risk factors for postpartum haemorrhage

Characteristics	Syntometrine n = 70 n (%)	Carbetocin n = 70 n (%)	P value
History of PPH	6 (8.5%)	11 (15.7%)	0.15
Grandmultipara	35 (50%)	36 (51.4%)	0.50
History of retained placenta	7 (10%)	13 (18.5%)	0.11
Twin pregnancy	7 (10%)	11 (15.7%)	0.22
Polyhydramnions	3 (4.2%)	3 (4.2%)	0.66
Fetal macrosomia	3 (4.2%)	3 (4.2%)	0.66
Augmentation of labour more than 4 hours	24 (34.2%)	26 (37.1%)	0.43
Maternal obesity	9 (12.8%)	11 (15.7%)	0.40
Anemia in pregnancy	3 (4.2%)	2 (2.8%)	0.50