

**HAEMODYNAMIC EFFECTS OF OXYTOCIN VERSUS
CARBETOCIN GIVEN AS INTRAVENOUS BOLUS TO
PARTURIENT UNDERGOING CAESAREAN DELIVERY
UNDER SPINAL ANAESTHESIA**

By

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HAEMODYNAMIC CHANGES BETWEEN CARBETOCIN VERSUS OXYTOCIN GIVEN
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Introduction : Postpartum haemorrhage (PPH) is one of the commonest causes of maternal morbidity and mortality. Uterine atony has been showed to be the cause of the most postpartum haemorrhage cases. In 2009 World Health Organization (WHO) in booklet for Prevention of Postpartum Haemorrhage has highly recommended active management of third stage of labour in attempt to reduce the incidence of postpartum haemorrhage by using uterotonic agents like oxytocin or carbetocin as part of active management of third stage of labour is highly recommended to prevent post partum haemorrhage. These medications can affect haemodynamic parameters including reduce in blood pressure and increase in heart rate. Carbetocin is an uterotonic agents licensed to be used in Malaysian Health Ministry since 2011.

Objective: The aim of this study were to compare the haemodynamic changes of carbetocin versus oxytocin on maternal hemodynamic parameters during caesarean section. This study also evaluate the side effects profile of both research drugs including comparing estimated blood loss during caesarean delivery when using either oxytocin or carbetocin.

Patients and Method: This is a prospective, randomized double blind study. There were one hundred twenty patients undergoing elective or emergency lower segment caesarean section under spinal anaesthesia. There were randomized to receive either IV oxytocin 5 IU or IV carbetocin 100 µg after delivery of baby. Vasopressor such as ephedrine or phenylephrine were advocated to maintain blood pressure at least around 15% of baseline before research drug is given. We compare the haemodynamic parameters such SBP, DBP, MAP and HR. The side effects profile also has been compared including the need of additional uterotonic agents

Results: It has been observed that there were reduction in systolic and diastolic blood pressure after both drugs are given however there were no statistically significant value between both drug's group ($p > 0.05$). Mean arterial pressure as well as heart rate also affected but the difference was not statistically significant. Estimated blood loss in group carbetocin were less (410.6 ± 142.3) and statistically significant when compared to group oxytocin (433.8 ± 258.4), $p < 0.05$. This study revealed that there were no significant differences in term of uterine tone score, side effects profile and need for additional uterotonics agents.

Conclusion : We conclude that there were rapid onset and offset of undesirable haemodynamic effects of either oxytocin 5 IU or carbetocin and the difference between oxytocin 5 IU and 100 µg carbetocin were minor and statistically not significant. The side effects profiles of both drugs are similar and not significant while it is proven that usage of carbetocin cause less blood loss compared to oxytocin. There were no significant values in usage of additional uterotonic agents between group oxytocin and carbetocin.

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LIST OF ABBREVIATIONS

ASA	American Society of Anaesthesiologist
bpm	beat per minute
cm	centimeters
DBP	diastolic blood pressure
dF	degree of freedom
HR	heart rate
HSB	Hospital Sultanah Bahiyah
IABP	Invasive Blood Pressure
IM	Intramuscular
IV	Intravenous
kg	kilogram
LSCS	lower segment Caesarean section
MAP	mean arterial pressure
mcg	microgram
mg	miligram
ml	militre
mmHg	milimeter mercury
PPH	postpartum haemorrhage
RM ANOVA	Repeated measure Analysis of Variance
SBP	Systolic blood pressure
SD	Standard deviation

CHAPTER 1 INTRODUCTION

Postpartum haemorrhage (PPH) is one of the commonest causes of maternal morbidity and mortality. Massive bleeding in PPH can be detrimental and affect the outcome of parturient. Uterine atony has been showed to be the cause of the most postpartum haemorrhage cases. In 2009 World Health Organization (WHO) in booklet for Prevention of Postpartum Haemorrhage has highly recommended active management of third stage of labour in attempt to reduce the incidence of postpartum haemorrhage. Therefore the usage of uterotonic drugs during Caesarean delivery has become essential to diminish the risk of PPH. Currently available uterotonic drug licensed to be use in Malaysia includes pitocin, syntocinon, syntometrine, carboprost and recently introduced is carbetocin.

Practice varies widely in the administration of oxytocin at Caesarean delivery. The British National Formulary presently recommends that oxytocin should be administered in a 5 IU dose by slow intravenous injection after delivery during Caesarean section (Formulary 2001). Currently in most maternity center in Malaysia, IV Oxytocin 5 IU is recommended as the prophylactic medication of choice to prevent uterine agony as this therefore will reduce the incidence of postpartum haemorrhage during Caesarean section. Oxytocin has a short half-life. Oxytocin is given bolus after delivery of baby and it need to be given as infusion for over 6 hours post bolus dose.

The haemodynamic effects of an oxytocin bolus consist of systemic vasodilatation, with hypotension, tachycardia, and an increase in cardiac output and pulmonary artery pressure, resulting in brief hypotension and tachycardia in a dose-dependent manner. oxytocin, given by rapid intravenous bolus, has the potential to cause dangerous haemodynamic collapse in women unable to mount compensatory increases in cardiac output such as those with hypovolemia and cardiac disease (Pinder *et al.*, 2002). Apart from that, large doses are also associated with nausea, vomiting, dysarrhythmia, ST segment changes, pulmonary edema and severe water intoxication (Moran *et al.*, 2001).

Recently new uterotonic drug namely carbetocin has been introduced to Malaysian Health Ministry hospitals in second half year 2011. Duratocin[®] (carbetocin injection) is a long-acting synthetic octapeptide analogue of oxytocin with agonist properties. It can be administered intravenously as a single dose immediately following delivery by Caesarean section under epidural or spinal anaesthesia, to prevent uterine atony and postpartum haemorrhage. The clinical and pharmacological properties of carbetocin are similar to those of naturally occurring oxytocin, another posterior pituitary hormone. In vitro studies, carbetocin was shown to bind to the oxytocin receptor with similar affinity as the natural peptide. Carbetocin elicited similar uteronic and galactogogic effects to oxytocin in animals and in vitro. Carbetocin was less potent than oxytocin, but its action was more prolonged up to 4-6 hours therefore carbetocin is only given bolus and no infusion needed. Study by Jetya *et al* showed that by using carbetocin, the usage of additional uterotonic agent is decreased. Although carbetocin cost more but looking at overall cost effectiveness, carbetocin is a drug of choice.

In one of the pilot study, Moertl *et al* in haemodynamic effects of carbetocin and oxytocin given as intravenous used non invasive monitoring that includes electrocardiography, ICG , beat to beat blood pressure by the vascular unloading were used to look in detail the haemodynamic effects of these two uterotonic drugs. Both oxytocin and carbetocin have comparable haemodynamic effects and are uterotonic drugs with an acceptable safety profile for prophylactic use. Minimal differences in the recovery phase beyond 70 seconds are in keeping with the fact that carbetocin has an extended half-life compared with oxytocin.

In Maternity Operation Theatre Hospital Sultanah Bahiyah, patient will be labeled as low risk group or high risk group developing PPH . Low risk group such as primigravida, with no significant obstetrical history will be given IV oxytocin 5 IU slow bolus followed by IV oxytocin 40 IU infusion over 6 hours. On the other hand if parturient are in the high risk group such as grandmultipara, prolonged labour, macrosomic baby, elderly primigravida, placenta praevia, twin gestation, IV carbetocin 100 µg will be given prophylactically. However if patient developed postpartum haemorrhage (PPH) that is when blood loss is more than 1000 ml or uterine contraction is unsatisfactory, Intramuscular carboprost 250 µg will be advocated. Expectant management of postpartum haemorrhage will be practiced accordingly by both anaesthetist & surgeon.

Pregnancy involved various changes since first trimester until third trimester. At term, cardiac output is 33% higher than normal with marked decrease in supine position owing

to obstruction of the inferior vena cava. This contributed by 15% increase in heart rate and 35% increase in stroke volume. As much as 20% of the cardiac output goes to uterus (800ml/min) (Sinclair 1963). Because of the cardiovascular changes associated with pregnancy and spinal anaesthesia, the use of the drugs especially those which cause hypotension and tachycardia must be done cautiously during delivery and Caesarean section.

Lower segment Caesarean section has gained its popularity over the last three decades. Caesarean delivery is preferred in situations where vaginal delivery is not feasible. The anaesthetic technique for Caesarean delivery can be either by giving general anaesthesia or regional anaesthesia. Regional anaesthesia either by giving epidural or single shot subarachnoid block is preferred since it is associated with less risk of failed intubation and neither will it contribute to the increased risk of bleeding. However, both regional anaesthesia techniques can cause hypotension secondary to loss of vasomotor tone. Various studies have been done to look at how to reduce the incidence of hypotension by adjusting the local anaesthetic dose, fluid preloading, type of fluid given and also choice of vasopressor was also taken into account.

The purpose of this study was to compare the haemodynamic profile including SBP, DBP, HR and MAP as well as side effects of oxytocin and carbetocin given during Caesarean delivery. There are many studies done looking into the effectiveness of carbetocin in terms of contractility of uterus and the ability to reduce the incidence of PPH,

however the haemodynamic analysis for this drug is lacking particularly in Asian population.

CHAPTER 2 LITERATURE REVIEW

2.1 PHYSIOLOGICAL CHANGES DURING PREGNANCY

The physiological adaptation to pregnancy causes significant changes in the cardiovascular system to allow the women to manage the increased metabolic requirements of the growing fetus. Whilst women with normal cardiac structure and function can adapt well, women with cardiac disease may decompensate which can lead to complications in pregnancy and even result in fetal and maternal death. The increase in work required by the heart is due to growing fetus with increasing oxygen consumption, enlarging uterus and breasts requiring greater oxygen demand, increase in work by mother due to 10–14 kg weight gain, placental bed acting like an arterio-venous fistula.

The physiological changes affect preload, intrinsic cardiac contraction, and the afterload. Cardiac preload is increased due to the increase in circulating volume which occurs from 6 weeks gestation and plateaus by the end of the second trimester at a level 50–70 % above the non-pregnant state. Red cell mass also increases but only by 40 % thus there is greater proportional increase in volume compared to red cell mass, leading to a relative haemodilution, the so called physiological anaemia of pregnancy. As a result of this blood volume increase, left ventricular end-diastolic (LVED) volume is increased which can be noticed on echocardiogram from 10 weeks' gestation. There is also a

corresponding increase in atrial and right ventricular chamber dimensions. This increase in blood volume creates particular problems for women with dilated cardiomyopathy and obstructive outflow lesions such as mitral stenosis or pulmonary hypertension.

Systemic vascular resistance (SVR) is the resistance of all the peripheral vasculature in the systemic circulation, and this should not be confused with pulmonary vascular resistance (PVR), which is the resistance only in the pulmonary circulation. SVR is measured by looking at the change in pressure across the systemic circulation from beginning to end and dividing it by the cardiac output. The afterload is the force against which the cardiac muscle has to contract and typically is reduced in pregnancy due to the fall in SVR. This reduction in resistance occurs from the 5th week of pregnancy and usually reaches its nadir between 20 and 32 weeks of gestation. After 32 weeks, the SVR rises again until term by which it has exceeded its pregnancy level.

The reduction in SVR is due to a combination of increased circulating vasodilators, namely prostacyclin (PGI₂) and to the diversion of blood into the low impedance uteroplacental circulation. There is significant increase in blood flow in the early stages of pregnancy; however, this is countered by a decrease in PVR, resulting in no net changes in pulmonary artery pressure.

The reduction in SVR results in increased flow to different anatomical beds and resulting physiological changes. Renal blood flow increases to 60–80 % above pre-pregnancy levels and peaks in the third trimester. This change coincides with a 50 % increase in

glomerular filtration rate (GFR), which is why normal blood levels of creatinine in pregnancy are reduced common in pregnancy.

Stroke volume is the volume of blood from the ventricle with each beat and is approximately 70mls in a healthy adult male. It is a major determinant of cardiac output (CO) as CO is the product of stroke volume and heart rate (HR), both of which are increased during pregnancy. CO increases by approximately 30–50 % reaching a peak at the end of the second trimester. The majority of CO increase is as a result of increase in stroke volume, though HR does contribute. HR is particularly important at the end of pregnancy, as the increase in stroke volume plateaus however the HR continues to rise. Women with fixed COs in the form of stenotic valve lesions are at risk of maternal and fetal compromise.

The increase in HR peaks in the late second or early third trimester and is usually 10–20 beats above pre-pregnancy levels, although there is a wide variation, and it is not uncommon to see women towards the end of their pregnancy with a sinus tachycardia. Maternal peak oxygen consumption can increase by 20–30 % at term as a result of both the increase in maternal and fetal tissue mass as well as the increase in cardiac and respiratory work. The increase in myocardial oxygen consumption may therefore trigger ischaemia in women with significant coronary disease.

Venous distension increases approximately to 150% during the course of gestation and the venous ends of capillaries become dilated, causing reduced blood flow. These

vascular changes contribute to delayed absorption of subcutaneously or intramuscularly injected substances. Distension of the extradural veins heightens the risk of vascular damage during institution of a regional block. The increased venous volume within the rigid spinal canal reduces the volume or capacity of the extradural and intrathecal spaces for local anaesthetics solutions. This will increase the cephalad spread of the injected drugs (Sinclair 1963).

Figure 2.1 Changes of plasma volume, heart rate, stroke volume and cardiac output during pregnancy

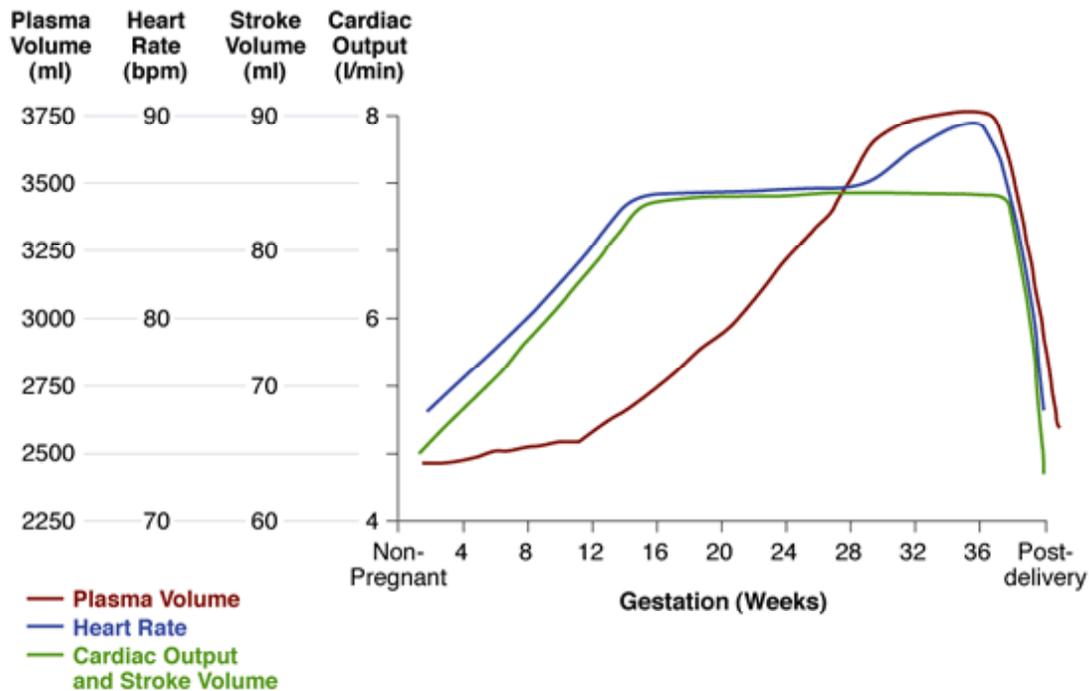


Table 2.1 Summary of changes during pregnancy simplified using arrow

Parameter	Changes at Various Times (week)					
	5	12	20	24	32	38
Heart rate	↑	↑↑↑	↑↑↑	↑↑↑	↑↑↑↑	↑↑↑↑
Systolic blood pressure	↔	↓	↓	↔	↑	↑↑
Diastolic blood pressure	↔	↓	↓↓	↓	↔	↑↑
Stroke volume	↑	↑↑↑↑↑	↑↑↑↑↑	↑↑↑↑↑	↑↑↑↑↑	↑↑↑↑↑
Cardiac Output	↑↑	↑↑↑↑↑	↑↑↑↑↑	↑↑↑↑↑	↑↑↑↑↑	↑↑↑↑↑
Systemic vascular resistance	↓↓	↓↓↓↓↓	↓↓↓↓↓	↓↓↓↓↓	↓↓↓↓↓	↓↓↓↓↓
Left ventricular ejection fraction	↑	↑↑	↑↑	↑↑	↑	↑

From : Langesaeter E, Dragsund M, Rosseland La.(2010) Regional anaesthesia for a Caesarean section in women with cardiac disease: a prospective study. *Acta Anaesthesiol Scand.* 2010 Jan;**54(1)**:46-54.

In summary, parturient experienced tremendous physiological changes including hormonal and effect psychological aspect as well. Furthermore there will more cardiocirculatory changes will occur during labour and delivery. As an anaesthetist, meticulous care should be taken together with obstetric team during managing this unique group of patients.

2.2 PHYSIOLOGICAL CHANGES DURING LABOUR AND DELIVERY

Pregnancy is state where there are changes involving almost all system in the body. These changes happen gradually within 37 weeks of pregnancy. During labour parturient experienced series of changes in order both mother and fetus to adapt condition during expulsion of fetus. This is a unique process involving several transient cardiocirculatory changes

2.2.1 Effect on cardiac output

CO increases up to 30% in the first stage of labour primarily because of increased stroke volume. Maternal pushing efforts in the second stage of labour can increase CO by as much as 50%. Compression of the uterus with contractions results in an increase in circulating blood volume and venous return to the heart, with concomitant increase in stroke volume. Pulmonary arterial venous oxygen difference also increases with contractions, addition of flow of blood from the maternal uterine vascular bed into the systemic circulation. Pain and anxiety leads to increased sympathetic tone with increased blood pressure and heart rate, which also contributes to the increased cardiac output.

2.2.2 Effects on Maternal Heart Rate

In contrast with cardiac output, the effects of contractions on maternal heart rate seem to be more variable. The observed differences in reported heart rate responses to uterine contractions relate to differences in maternal position and pain control during labour, as well as individual variation.

2.2.3 Effects on Maternal blood pressure

Both systolic and diastolic blood pressure increase with uterine contractions and this increase seem to precede a contraction by up to 8 seconds. The maximal increase occurs in the second stage of labour. Because peripheral resistance changes only slightly during labour, the increase in blood pressure is attributed to increased cardiac output. As expected, the hemodynamic effects of uterine contractions are less pronounced in the left lateral recumbent position. Oxygen consumption increases about 3-fold during uterine contractions, with its mean value increasing gradually to levels 100% higher than those before labour.

2.2.4 Effects of Maternal Anesthesia

Uterine contraction will cause tachycardia during second stage of labour and it can be additive due to pain during contraction and this can occur if local anaesthesia is inadequate. Both the systolic and diastolic blood pressure shows a mild gradual increase during the first stage of labour and a significant increase during the second stage. These changes are associated with a progressive increase in stroke volume toward a peak immediately following delivery. In contrast, regional anesthesia however can obtund the extreme changes of blood pressure and heart rate during first and second stage of labour. Many patients with regional anaesthesia have transient hypotension early on, which can be mitigated with pre induction volume load. On the other hand, stroke volume in patient under regional anaesthesia remains constant throughout labour but increases rapidly after delivery. Mean blood loss does not seem to be affected by type of anaesthesia at delivery. In patients with underlying cardiac disease, anaesthesia during labour and delivery can pose unique challenges. Continuous lumbar epidural anaesthesia with or without

narcotics, is frequently optimal. Limited sympathetic blockade and its effects on preload and afterload can be helpful in patients with mitral valve lesions. In patients with more complex lesions, anesthesia options must be considered on a case-by-case basis using a multidisciplinary approach.

2.2.5 Haemodynamic effects during Caesarean delivery

Transient maternal hypotension can occur in up to 30% of women undergoing regional anaesthesia for Caesarean section, but most women undergoing Caesarean section under epidural anaesthesia remain stable haemodynamically. Blood pressure typically declines moderately after anaesthesia induction, but then remains constant throughout operation. In addition, heart rate and stroke volume remain constant. Following delivery, cardiac output increases about 25% more than baseline, with a stable HR. In contrast, Caesarean section under spinal anaesthesia is associated with significant cardiovascular changes and should be used with extreme caution in patients with heart disease. Hemodynamic fluctuations during Caesarean section were less with thiopental, nitrous oxide, and succinylcholine anaesthesia. Thus, balanced anaesthesia with thiopental, nitrous oxide, and succinylcholine, or epidural anaesthesia without epinephrine, are preferred in patients with limited cardiac reserves.

After delivery of baby, mother's haemodynamic changes once again challenged due to administration of uterotonic agent. These agents such as oxytocin, carbetocin, ergometrine or prostaglandin can cause transient tachycardia and hypotension secondary to vasodilatation. These changes will be explained in detail in next topic.

2.3 HEMODYNAMIC CHANGES DURING POSTPARTUM PERIOD

There will be 60% to 80% increase in cardiac output occurs immediately after delivery, followed by a rapid decrease within 10 minutes to values approaching normal within 1 hour postpartum. In addition, systemic vascular resistance decreases. This high output state is likely caused by the transfer of blood from the uterus into the systemic circulation (autotransfusion) in conjunction with improved venous return caused by decreased vena caval compression and the rapid mobilization of extracellular fluid. Placental separation in the third stage of labour does not cause any further hemodynamic changes. Even though childbirth can result in a mean blood loss of 1000 ml or more, patients are protected by the significant blood volume expansion during pregnancy. In women with postpartum haemorrhage, compensatory effect stroke volume decreases and heart rate increases, whereas blood pressure and cardiac output remained stable. Equally important, levels of atrial natriotic peptide increase durring postpartum. Atrial natriotic peptide have potent diuretic effects, and help mediate the diuresis noted in the early postpartum period. Summary of changes during postpartum period is shown below.

Table 2.2 Cardiovascular changes during pregnancy, peripartum, and postpartum

	Pregnancy	Peripartum	Postpartum
Blood volume	↑	↑	↓
Systolic blood pressure	↓	↑	↑
Diastolic blood pressure	↓	↑	↑
Systemic vascular resistance	↓	↑	↑
Heart rate	↑	↑	↓
Stroke volume	↑	↑	↓
Cardiac output	↑	↑	↓

From: Sinclair J.D (1963) Cardiovascular changes during pregnancy. *Mod Trends Hum Repro Physiol*, **15**, 175-89.