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Carbetocin Versus Oxytocin in Prevention of Atonic Postpartum Hemorrhage

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ABSTRACT

Background: Pregnancy related deaths are considered one of the chief causes of premature women's death worldwide as about 500,000 ladies die yearly from this cause, about 25.0% of these mortalities are due to hemorrhage.

Aim of the work: Comparison of the safety and effectiveness of carbetocin over oxytocin in prevention of postpartum Hemorrhage due to uterine atony after vaginal deliveries and cesarean sections.

Patients and Methods: This computerized random cross sectional prospective comparative study included a total 400 pregnant women who were going to deliver, attending at Obstetric and Gynecological Department at El-Matara Teaching Hospital in Corporation with Obstetric and Gynecological Department, Faculty of Medicine, Al-Azhar University. This study was conducted between October 2017 to October 2018.

Results: Carbetocin was proved statistically to be more effective in preventing uterus atony and thereby PPH in comparison with oxytocin.

Conclusion: It could be concluded that carbetocin is a better uterotonic agent in comparison with Oxytocin in management of postpartum hemorrhage due to uterine atony after delivery either vaginal or cesarean section as it decreases incidence of occurrence of PPH and post-partum blood loss.

Keywords: Carbetocin; Oxytocin; Atonic Postpartum Hemorrhage

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INTRODUCTION

One of the most leading causes of pregnant women morbidity and mortality is postpartum hemorrhage "PPH" as it causes about 140,000 deaths yearly worldwide. Because of PPH a woman dies every 4 minutes every day, PPH is the fifth leading cause of women mortality.

Postpartum hemorrhage can be classified into primary and secondary PPH, the Primary PPH can be defined as blood loss of ≥ 500 ml in case of vaginal delivery and loss of ≥ 1000 ml in case of Cesarean section "CS" in the first 24 hours of delivery, while the Secondary PPH can be defined as excessive vaginal bleeding or heavy discharge of lochia that occurs at least 24 hours after the end of the third stage of labor.²

The primary PPH can be also defined as the amount of blood loss that can cause hypovolemia, drop of hematocrit by 10% or increase the need for blood transfusion regardless the route of delivery.³

The Risk factors that can increase the incidence of PPH include; previous PPH, fetal macrosomia, multiple high risk pregnancy, primigravida, grand multi-parity "> 5", older maternal age, preterm delivery, injuries of the genital tract, absence of prophylactic oxytocics usage for prevention of

PPH, induction of labor, CS delivery and intra-uterine fetal deaths "IUFD".⁴

It is known that no woman is immune against PPH and PPH unpredictably occurs.⁵ It was revealed in many studies that PPH is mainly occurred due to uterine atony as it causes up to 80% of these cases.³ So the Uterotonic drugs that increase the uterine muscle tone were initially used for PPH treatments.⁶

The most widely used uterotonic agent is oxytocin. In order to achieve sustained uterotonic activity it is used as a continuous infusion because of its short half-life "4 – 10 min".⁷

Carbetocin is a long-acting synthetic agonistic analogue of oxytocin which has a longer half-life leading to longer and prolonged pharmacological effects. These prolonged effects offer medical advantages over oxytocin in the third stage management.

As regard side effects, no significant difference was reported between both carbetocin and oxytocin but it may have advantage over syntometrine.⁸

The aim of the study was comparing between effectiveness and safety of carbetocin and oxytocin in preventing of atonic PPH after vaginal deliveries and cesarean sections.

PATIENTS AND METHODS

This computerized random cross sectional prospective comparative study included a total of 400 pregnant women who were going to deliver, attending at Obstetric and Gynecological Department at El-Mataria Teaching Hospital in Corporation with Obstetric and Gynecological Department, Faculty of Medicine, Al-Azhar University. Written informed consent from all the subjects were obtained. This study was conducted between October 2017 to October 2018. Approval of the Ethical Committee, Faculty of Medicine, Al-Azhar University was obtained.

The included subjects were randomly divided into two groups; Group I (Carbetocin group) included 200 women who received carbetocin and delivered either by cesarean section (CS) or vaginal, Group II (Oxytocin group) included 200 women who received oxytocin and delivered either by cesarean section (CS) or vaginal.

The following was done to all selected patients: 1- complete Medical History: Personal history, Past history, Menstrual and Obstetric and history, and Family history. 2- Full general medical examination: including cardiological, chest, abdominal and monitoring vital data (heart rate, systolic and diastolic blood pressure). 3- Obstetrical Examination: Fundal level to correlate with GA, Obstetric grip. And Obstetric Ultrasound for viability, fetal biometry, placentation, presentation and position. 4- Vaginal Examination: For assessing the cervical effacement, dilation, fetal presentation, occipit, and exclude caput succedaneum or any sort of mechanical obstruction. Vaginal examination was done under complete aseptic conditions by sterile gloves. 5- Routine preoperative investigations: Complete blood count (CBC), kidney and liver function tests. These investigations were done to exclude patients with abnormal kidney or liver functions or hidden general chronic medical diseases.

Intra Operative: 1- In cases delivered with CS:

All patients was given 500 ml crystalloid as an IV bolus then a standardized spinal anaesthesia was done by a needle sized 25G. All patients was placed in sitting of leftlateral position. The anesthetic solution consisted of 0.5% hypertonic bupivacaine “2 ml”, fentanyl “10 – 20µg” and free morphine “0.1 mg”. Anaesthesia was done up to the level of Thoracic vertebrae 5. The Association of Anesthetists’ of Great Britain and Ireland “AAGBI” guidelines was used for monitoring. Blood loss was replaced at operation when needed. A standardized approach to CS was performed. Surgeons were requested to do a standard procedure that specifies transverse lower segment cesarean section two layer closure of the uterine incision, and to avoid delivering the uterus for suturing unless clinically indicated. 2- Active management of the 3rd stage of

labor was done: The uterotonic agent was given with delivery of the anterior shoulder. Soon after birth we clamped and cut of the umbilical cord. Controlled cord traction was applied with applying a simultaneous counter-pressure to uterus through abdomen to avoid its inversion.

Intervention and giving the study drugs: Selection of the study drug that was given to each patients was done by computerized random sample selection. 1) Carbetocin group: patients was given 1ml solution of 100 µg carbetocin by slow intravenous injection over 2 minutes after the C-shaped incision of the uterus is done in CS or after crowning of the fetal head in vaginal delivery. 2) Oxytocin group: patients was given 20 IU oxytocin by I.V. infusion over one hour after the C-shaped incision of the uterus is done in CS or after crowning of the fetal head in vaginal delivery.

Local Examination Following Delivery: To exclude traumatic PPH e.g.: extension of episiotomy, cervical, vaginal, Para urethral tears or retained either placental or membranous parts.

Follow up the patients postoperatively: for 24 hours after delivery. 1- Vital data (HR, SBP and DBP). 2- Hemoglobin concentration. 3- Hematocrit percent.

Outcomes:

Primary outcomes: The incidences of atonic postpartum hemorrhage between both groups.

Secondary outcomes: Calculation of amount of intrapartum and postpartum blood loss and compare between the incidences of major obstetric hemorrhage ($\geq 500 - 1000$ ml) following use of different uterotonic agents. Change in hemoglobin and hematocrit value post versus pre delivery between groups. To assess the need for blood transfusion. The need for further uterine intervention for treatment of PPH. Any fetal or maternal morbidity e.g. development of severe anemia, need for blood transfusion, Hysterectomy....etc.

Statistical methods:

The collected data was tabulated and statistically analyzed by a statistical package of SPSS version 23.0 for windows. The parametric numerical data was described as mean, SD and range, while non-parametric numerical data was described as median and non-numerical data was described as frequency and percentage. Analytical Statistics: the significant difference between groups was assessed by the student T test. Level of significance reported as following $P > 0.05 =$ Non-significant. $P < 0.05 =$ Significant and $P < 0.01 =$ Highly significant.

RESULTS

Variable	Group I (Carbetocin) (N = 200)	Group II (Oxytocin) (N = 200)	P-value
Maternal Age: (years)			
- Mean ± SD	28.04 ± 2.9 (20 – 36)	28.74 ± 2.5 (21 – 35)	0.229 (NS)
- Range			
Body Mass Index: (Kg/m²)			
- Mean ± SD	26.02 ± 2.2 (23 – 32)	25.87 ± 2.15 (22 – 31)	0.237 (NS)
- Range			
Gestational Age (GA): (weeks)			
- Mean ± SD	38.8 ± 1.3 (37 – 41)	38.61 ± 1.2 (37 – 41)	0.690 (NS)
- Range			
Parity			
- Mean ± SD	2.08 ± 1.18 (0 – 5)	2.03 ± 1.3 (0 – 4)	MW 0.631 (NS)
- Range			

Tables 1: Comparison between both studied group regarding demographic, anthropometric and obstetric data.

No significant difference between both groups of the study as regard age, BMI, GA, and parity with p-value: 0.229, 0.237, 0.690 and 0.631 respectively. Table (1).

Variable	Group I (Carbetocin)		p-value
	Pre labor	Post labor	
Pulse:	84.8 ± 7.05	85.78 ± 7.14	0.168 (NS)
Systolic Blood pressure:	110.1 ± 2.3	108.9 ± 9.8	0.093 (NS)
Diastolic Blood pressure:	67.05 ± 1.15	65.9 ± 9.7	0.097 (NS)
HB% concentration:	10.66 ± 0.76	9.94 ± 0.80	<0.001 (HS)
HCT	31.76 ± 2.2	29.8 ± 0.32	<0.001 (HS)

Table 2: Comparison of vital data, Hb concentration, Hematocrit and percentage of difference pre and post in Carbetocin group.

No significance difference between pre and post 2 hour after administration of therapeutic drugs hemodynamic data including HR, SBP and DBP within carbetocin group with p-value: 0.168, 0.093 and 0.097 respectively. There was a statistical significance difference between pre- and post-labor hemoglobin concentration and hematocrit percent with the carbetocin group with p-value: <0.001 for each. Table (2).

Variable	Group II (Oxytocin)		p-value
	Pre labor	Post labor	
Pulse:	86.01 ± 7.5	87.4 ± 9.7	0.110 (NS)
Systolic Blood pressure:	110.4 ± 1.26	109.9 ± 8.46	0.409 (NS)
Diastolic Blood pressure:	67.17 ± 0.05	66.7 ± 6.5	0.307 (NS)
HB (g/dl):	10.75 ± 0.83	9.7 ± 0.9	<0.001 (HS)
HCT (%)	31.68 ± 2.1	29.2 ± 1.9	<0.001 (HS)

Table 3: Comparison of vital data, Hb concentration, Hematocrit and percentage of difference pre and post in oxytocin group.

No statistical significance difference between pre and post 2 hour after administration of therapeutic drugs hemodynamic data including HR, SBP and DBP within oxytocin group with p-value: 0.110, 0.409 and 0.307 respectively. There was a statistical significant difference between pre- and post-labor hemoglobin concentration and hematocrit percent with the oxytocin group with p-value: <0.001 for each. Table (3).

DISCUSSION

The included studied 400 pregnant women were randomly divided into two groups; Group I (Carbetocin group) included 200 women who received carbetocin and delivered either by cesarean section (CS) or vaginal, Group II (Oxytocin group) included 200 women who received oxytocin and delivered either by cesarean section (CS) or vaginal.

Group II (oxytocin group) was associated with significant increased incidence of atonic postpartum hemorrhage (p: 0.006) and amount of blood loss (p: 0.019) when compared with group I (carbetocin group). Also group II was associated with significantly lower Hemoglobin concentration (p: 0.005) and Hematocrit percent (p: <0.001) that was measured 24 hours after labor, while the difference in Hb and HCT between pre and post-labor findings was significantly higher in group II than in group I (p: <0.001 for each).

Within group I, our result showed that the 24-hour post-labor findings of both Hb concentration and HCT percent were significantly lower in comparison with their pre-labor findings (p: <0.001 for each). Similar findings were reported with group II.

A comparison was done between those delivered vaginally in both studied groups (I and II) showed that patients in group II had a significant higher amount of blood loss (p: 0.001). Also group II was associated with significantly lower hemoglobin concentration (p: 0.047) and hematocrit percent (p: 0.002) that was measure 24 hours after labor, while the difference in Hb and HCT between pre and post-labor findings was significantly higher in group II than in group I (p: <0.001 for each)

Another comparison was done between those delivered by CS in both studied groups (I and II) and our results showed patients in group II had a significant higher amount of blood loss (p: <0.001), also group II was associated with significantly lower Hemoglobin concentration (p: 0.019) and Hematocrit percent (p: 0.021) that was measure 24 hours after labor, while the difference in Hb and HCT between pre and post-labor findings was significantly higher in group II in comparison with group I (p: <0.001 and 0.003 respectively).

From these findings, it could be concluded that carbetocin is effective in prevention of uterine atony and thereby PPH in comparison with oxytocin and this could be attributed to that carbetocin produces a tetanic uterine contraction 2 minutes after IV injection of 8 – 30 mg of IM injection of 10 – 70 mg which persist for only one minute. While, it produces a rhythmic contraction that persist for 60 and 120 min respectively after IV and IM injections.

The explanation

Carbetocin was found to have a longer half-life than that of oxytocin, this leads to increased amplitude and frequency of uterine contractions⁹.

Our results were in agree with those of Maged et al.² who reported in their study on 200 high risk pregnant women undergoing vaginal delivery that there was a statistical significance difference between both studied groups as regard occurrence of PPH with p-value: 0.037. Also, they reported a statistical significance difference between both groups regarding bleeding amount (ml) with p-value: 0.03. Regarding hemoglobin concentration, they reported that there was no significance difference between both studied groups regarding hemoglobin concentration before delivery with p-value: 0.581. While there was a statistical significance difference between both studied groups regarding Hb concentration 24 hours after delivery with p-value: 0.04. They also reported that there was a significance difference regarding hemoglobin difference (before and after delivery) with p-value: <0.001.

Our results were also in agreement with those of Debbie-Lyn¹⁰ who reported in their Randomized single blind controlled trial on 70 pregnant women undergone Cesarean Section, that in the carbetocin, there was a significance decrease in the post-operative Hb and HCT levels from the baseline preoperative level. Also, there was a significance decrease in Hb and HCT levels postoperatively from the baseline levels in the oxytocin group. Also they reported that

the in the carbetocin group postoperative hemoglobin and hematocrit levels were higher than in the oxytocin group with a statistical significant difference “p-value: <0.001”.

In contrast to our findings regarding amount of blood loss, Larciprete et al.¹¹ reported in their study on 102 pregnant women undergoing caesarean section that no significance difference between both studied groups regarding estimated blood loss and the incidence of primary PPH.

In consistence with our findings regarding Hb concentration and HCT percent was Maged et al.¹² who reported in their study was on 100 pregnant women who underwent vaginal delivery that there was no significant difference between Hb before delivery in carbetocin group versus that in oxytocin group with p-value: 0.55. And there was no significance difference between both groups regarding Hb 24 hour after delivery with p-value: 0.645. They also reported that there was no significance difference as regard Hb difference (before and after delivery) (g/dl) between both groups with p-value: 0.529.

Our results showed that no significance difference was observed between both groups post-labor anemia with p-value: 0.08. Also, regarding need for blood transfusion, no statistical difference was found between both groups with p-value: 0.2.

In agree with our results Maged et al.¹² reported that no statistically significance difference between both groups regarding the need for blood transfusion (12% vs 18%) with p-value: 0.401.

CONCLUSION

It could be concluded that in comparison with oxytocin, carbetocin was found to have a better uterotonic effects in management of PPH due to uterine atony after delivery either vaginal or CS as it decreases incidence of occurrence of PPH and post-partum blood loss.

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