Carbetocin versus Oxytocin in Cesarean Section in a Patient with a High Risk of Postpartum Hemorrhage

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Abstract: Aim: To compare the efficacy of oxytocin and Carbetocin to prevent the PPH in cesarean section at high risk of primary postpartum hemorrhage. **Material and Methods:** A Prospective Randomized Comparative Study was carried out at Sayed Galal and Al Hussein Hospitals at Al Azhar University in Cairo. 200 pregnant women with high risk of primary postpartum hemorrhage undergoing cesarean section were involved in the study. Patients divided into two groups: Group A (Carbetocin): included (100) pregnant women undergoing elective cesarean section with use a bolus of 100 µg Carbetocin IV at delivery of the anterior shoulder and Group B (Oxytocin): included (100) pregnant women undergoing elective cesarean section with use of 20 IU of oxytocin in 1000 ml of 0.9% NaCl solution IV (150 mL/hour) at delivery of the anterior shoulder. **Results**: The present study showed that Hb decrease at 12 hours from delivery in the oxytocin group and Hb level was significant (- 0.6 g/dl vs - 1.2 g/dl, p 0.03). As regards incidence and severity of PPH; In fact, we did not demonstrate any difference in the amount of blood loss after cesarean section but within 2 hours and 24 hours, we showed in the oxytocin group higher degree of blood loss than Carbetocin group and there was no significant difference. Otherwise, no other significant difference between two groups regarding incidence of PPH, need for additional uterotonic drugs (with less need in Carbetocin group than oxytocin group) nor incidence of other side effects like headache. **Conclusion**: single injection of Carbetocin appears to be more effective than a continuous infusion of oxytocin to maintain adequate uterine tone. Further studies are needed to verify our findings.

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1. Introduction

Prevention of post-partum haemorrhage (PPH) is a major issue due to its impact on maternal morbidity and mortality. Postpartum hemorrhage (PPH) is the leading cause of maternal death worldwide, with an estimated mortality rate of 140 000 women per year, or 1 maternal death every 4 minutes **(Rani, 2017)**

PPH occurs in 5% of all deliveries and is responsible for a major part of maternal mortality **(Ngwenya, 2016)**.

The majority of these deaths occur within 4 hours of delivery, which indicates that they are a consequence of the third stage of labor**(Bajwa et al., 2012)** Non-fatal PPH results in further interventions, iron deficiency anemia, pituitary infarction (Sheehan's syndrome) with associated poor lactation, exposure to blood products, coagulopathy, and organ damage with associated hypotension and shock **(Dahlke et al., 2015; Girard et al., 2009)**.

Since all parturient women are at risk for PPH, care providers need to possess the knowledge and skills to practice active management of the third stage of labor, to prevent PPH and to recognize, assess, and treat excessive blood loss**.** Cesarean section is a recognized risk factor for PPH and the worldwide cesarean delivery rate is increasing**(Wormer & Bryant, 2018)**.

Systematic reviews have concluded that active management of the third stage of labor, particularly the prophylactic use of uterotonic agents can significantly decrease the incidence of postpartum hemorrhage compared with that of expectant management. An ideal uterotonic agent should promote prompt, strong and sustained uterine contractions after intramuscular (IM) injection without any significant adverse effects**(Leung et al., 2006; Magee et al., 2014)**.

The administration of oxytocics after the delivery of the neonate reduces the likelihood of PPH and 5 IU oxytocin by slow intravenous injection is currently recommended for all cesarean sections**.** However, the use of additional oxytocic medication is common, to arrest bleeding, or prophylactically if there are risk factors for PPH**(Ghosh et al., 2013)**.

Carbetocin is a synthetic analog of human oxytocin with structural modifications that increase its half-life thereby prolonging its pharmacological effects. Two double-blind Randomised trials compared 100 micrograms Carbetocin (the licensed dose) with different combinations of oxytocin, bolus and infusion, following cesarean section. The first trial

found that significantly more women needed additional oxytocic interventions in the oxytocin group. The second trial found no significant differences in the intraoperative blood loss**(Dell-Kuster et al., 2016)**.

In our study, we investigated the efficacy of Carbetocin vs. oxytocin for prevention of PPH in women undergoing cesarean section with high risk of postpartum hemorrhage.

Patients and Methods

Settings:

Prospective Randomized Comparative Study was conducted at the Obstetrics and Gynecology Department of Sayed Galal and Al Hussein Hospitals at Al Azhar University in Cairo. 200 pregnant women with high risk of primary postpartum hemorrhage undergoing cesarean section were recruited and they were randomized by random method into two groups: Group A (**Carbetocin**) included 100 pregnant women undergoing elective cesarean section with use a bolus of 100 µg IV Slowly over2 minute at delivery of the anterior shoulder. Group B (**oxytocin**) included 100 pregnant women undergoing elective cesarean section with use of 20 IU of oxytocin in 1000 ml of 0.9% NaCl solution IV (150 mL/hour) at delivery of the anterior shoulder.

Selection Criteria:

Women undergoing elective cesarean sections at term and Presence of risk factors for primary postpartum hemorrhage: Uterine fibroids, Anemia, multiple pregnancy, past history of PPH, Fetal macrosomia or Polyhydramnios were included in this study. Pregnant women with hypertension, preeclampsia, Cardiac, renal or liver diseases, Epilepsy and general anesthesia, Women with history of hypersensitivity to Carbetocin or oxytocin, blood disease e.g thrombocytopenia, anticoagulants or placenta Previa were all excluded from this study.

Every patient subjected to careful and detailed history taking, general examination, abdominal examination and vaginal examination.

Laboratory processing:

Complete blood count, Rh typing, Coagulation profile (Prothrombin time, Partial Thromboplastin Time, INR), Liver function tests and Renal function tests.

Ultrasound study:

Using trans abdominal ultrasound scan to Confirm gestational age and to detect any risk factors for postpartum hemorrhage.

Intervention:

Participants received either a bolus of 100 µg IV (group A) or 20 IU of oxytocin in 1000 ml of 0.9% NaCl solution IV (group B) at delivery of the anterior shoulder & spinal anesthesia for all patient.

Follow up:

Hemoglobin concentration hematocrit value noted before cesarean sections and 24 hours' postpartum. The differences between pre- and post C.S values were calculated in each group. The uterine tone and size were assessed by using a hand resting on the fundus and palpating the anterior wall of the uterus. The presence of a boggy uterus with either heavy vaginal bleeding or increasing uterine size can suspect diagnosis of uterine atony. Need for additional uterotonic drug in each group population were reported and tabulated. Incidence of postpartum hemorrhage was reported and tabulated. All participants operated under spinal anesthesia. All cesarean section procedures performed by surgeons who at least have 2 years' experience in practicing cesarean sections (senior resident).

Statistical analysis:

Data were analyzed using Statistical Program for Social Science (SPSS) version 23.0. Quantitative data were expressed as the mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage. P value < 0.05 is significant.

Ethical consideration:

Agreement for this study was obtained from the hospital's ethical committee, and an informed oral and written consent were taken from all patients included in the study prior surgery after a very clear explanation of both procedure, adequate providing of information about the study necessities, purpose, and dangers.

3. Results

Table1: demographic data of patients:

Characteristics	Groups	N	Mean	Sd	Minimum	Maximum	P-Value
Age	Carbetocin	100	26.03	4.206	18	37	0.31
	Oxytocin	100	27.27	6.362	18	39	
Gestational Age	Carbetocin	100	39.23	0.898	38	41	0.5
	Oxytocin	100	39.03	0.964	38	41	
Gravidity	Carbetocin	100	2.53	1.196	1	5	0.38
	Oxytocin	100	2.87	1.697	1	6	
Parity	Carbetocin	100	1.23	1.135	0	4	0.36
	Oxytocin	100	1.53	1.408	0	4	
BMI	Carbetocin	100	29.87	1.174	27.89	32.32	0.08
	Oxytocin	100	29.01	1.217	25.86	31.6	

There were no significant statistical differences among the two groups with regard to (maternal age, gestational age, gravidity, parity, BMI and pulse pre [P >0.05]).

Table 2: Different risk factors among the two groups.

Risk Factors		Count	P-Value
History Of Pph	Carbetocin	7	0.93
	Oxytocin	10	
Fetal Macrosomia	Carbetocin	7	0.68
	Oxytocin	6	
Twins	Carbetocin	4	0.13
	Oxytocin	5	
Uterine Fibroids.	Carbetocin	2	0.21
	Oxytocin	3	
Polyhydramnios.	Carbetocin	4	0.5
	Oxytocin	5	
Maternal Anemia	Carbetocin	2	0.46
	Oxytocin	3	

There was non-significant difference regard to risk factors between the two groups (P >0.05).

Table 3: Haemoglobin, hematocrit, and platelets levels before and after cesarean section.

	Carbetocin (A)		*Oxytocin (B)*		
	Mean	**Range**	**Mean**	**Range**	**P-value**
Pre-Operative Hb (median interquartile ranges)					
Hb (g/dl)	**11.34**	**(11.01 - 11.98)**	**11.8**	**(11.2 - 12.13)**	**0.23**
Ht (%)	**34.6**	**(31.8 - 35.82)**	**33.9**	**(31.03 - 35.9)**	**0.61**
PLT	**225**	**(187 - 268)**	**207**	**(152 - 237)**	**0.06**
Post-Operative Hb Drop (median interquartile ranges)					
Hb 2 h after CS (g/dl)	**-0.5**	**(-1.1; -0.1)**	**-0.7**	**(-1.3; -0.3)**	**0.52**
Hb 12 h after CS (g/dl)	**-0.6**	**(-1.2; 0.0)**	**-1.2**	**(-1.9; -0.4)**	**0.03**
Ht 2 h after CS (%)	**-1.5**	**(-2.7; -0.1)**	**-1.9**	**(-4.0; 0.5)**	**0.31**
Ht 12 h after CS (%)	**-1.33**	**(-3.4; 0.3)**	**-1.7**	**(-5.1; 0.3)**	**0.13**
PLT 2 h after CS	**-19**	**(-50; 0)**	**-7**	**(-27; 1)**	**0.41**
PLT 12h after CS	**-17**	**(-44; 0)**	**-13**	**(-28; 8)**	**0.74**

In both study groups hemoglobin levels before and after 2 hours apart from delivery were similar, confirming no significant difference in the level of blood loss, although we found a roughly lower Hb decrease at 12 hours from delivery in the Carbetocin group and Hb level was significant (- 0.6 g/dl vs - 1.2 g/dl, p 0.03).

Table 4: Comparison between two groups as regards need for additional uterotonics drugs.

Group		Carbetocin	Oxytocin	P-Value
Postoperative Syntocinon		**25**	**29**	**0.1**
Additional Uterotonic Drugs		**23**	**33**	**0.06**
Intraoperative Carbetocin		**13**	**14**	**0.5**
Postoperative Ergometrine		**14**	**19**	**0.1**
Intraoperative Ergometrine		**15**	**17**	**0.07**
		Carbetocin	**Oxytocin**	**P-Value**
Further Treatment	**Uterine Artery Ligation**	**8**	**12**	**0.15**
	Compression Sutures	**8**	**12**	**0.31**
	Hysterectomy	**0**	**1**	**1.0**

When we tested the need for additional uterotonic drug comparing both groups it was non-significant.

Table 5: additional measures either for prevention or further treatment of postpartum hemorrhage.

		Carbetocin	Oxytocin	P Value
Further Treatment	**Uterine Artery Ligation**	**8**	**12**	**0.15**
	Compression Sutures	**8**	**12**	**0.31**
	Hysterectomy	**0**	**1**	**1.0**

Uterotonics failed to prevent and control PPH in 20 patients (8 patients in Carbetocin group and twelve patients in oxytocin group) who required further surgical management. In Carbetocin group: eight patients had atonic postpartum hemorrhage which managed surgically by bilateral uterine artery ligation followed by compression sutures. In oxytocin group: twelve patients had atonic postpartum hemorrhage which managed surgically by bilateral uterine artery ligation followed compression sutures, hysterectomy was the final solution for intractable hemorrhage in one of them.

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4. Discussion

Prevention of post-partum haemorrhage (PPH) is a major issue due to its impact on maternal morbidity and mortality. The primary PPH is defined as blood loss more than 500 mL after vaginal delivery and more than 1000 mL after caesarean section, that occurs in the first 24 hours after delivery **(Malabarey et al., 2011)**

Several uterotonic agents can be used for prevention and treatment of postpartum hemorrhage. Including Oxytocin, Ergot alkaloids, Syntometrine and Prostaglandins. ***Soltani et al.,*** demonstrated in their study in Egypt that misoprostol is a proven potent uterotonic agent **(Soltani, Hutchon, & Poulose, 2010)**

The aim of our study was to compare the efficacy of oxytocin and Carbetocin to prevent the PPH in caesarean section at high risk of primary post-partum haemorrhage.

The present study showed that as regards the demographic variables; results of comparison between two groups as regards the mean values of maternal age, gestational age, gravidity, parity, BMI and pulse pre were statistically non-significant [P >0.05]. Also we did not note any statistical significant relation among the two groups as regard history of postpartum haemorrhage.

Population profile regards different risk factors among the two groups and indication to elective caesarean section were similar for each group, however in oxytocin group the main indication has been the history of PPh with non-significant difference regard to risk factors between the two groups (P >0.05).

In both study groups hemoglobin levels before and after 2 hours apart from delivery were similar, confirming no significant difference in the level of blood loss. But, we found noted Hb decrease at 12 hours from delivery in the oxytocin group and Hb level was significant (- 0.6 g/dl vs - 1.2 g/dl, p 0.03).

Attilakos et al., have randomized 377 women undergoing cesarean sections to receive either IV Carbetocin 100 mg or IV oxytocin 5 IU after the delivery of the baby. The Carbetocin group needed significantly less uterotonic results, which agrees with our findings**(Attilakos et al., 2010)**

As regards incidence and severity of PPH; In fact, we did not demonstrate any difference in the amount of blood loss after caesarean section but within 2 hours and 24 hours, we showed in the oxytocin group higher degree of blood loss than Carbetocin group and there was no significant difference in the amount of estimated blood loss and in the incidence of primary post-partum haemorrhage (>1000 ml) in both groups.

A study investigated the efficacy of Carbetocin vs. oxytocin for prevention of uterine atony in high-risk women undergoing delivery by caesarean section. Significantly fewer women experienced uterine atony after caesarean delivery with Carbetocin (8%) versus oxytocin (19%). Blood loss>500 ml was only observed in women who received oxytocin **(Begum et al., 2016; Chen et al., 2018)**

Our analysis tested the need for additional uterotonic drug comparing both groups it was non-significant. but, with less need in Carbetocin group than oxytocin group.

Borruto et al., demonstrated that in the Carbetocin group, 20 of the 52 women (38.4%) required at least one uterine massage compared to 30 of the 52 women (57.7%) in the oxytocin group (P < 0.01). Overall, uterotonic intervention was clinically indicated in two of the women (3.8%) receiving Carbetocin compared to five of the women (9.6%) given an IV oxytocin infusion (P < 0.01). The odds ratio of treatment failure requiring oxytocic intervention was 1.83 (95% confidence interval, CI, 0.9-2.6) times higher in the oxytocin group compared with the Carbetocin group.

This was in agreement with our thesis despite different mode of delivery. Mode of delivery is an

important factor that can influence the treatment outcome. May be uterine scar make uterus respond in a different manner than in vaginal delivery. Thus, it is recommended to undertake more studies including patients with different modes of delivery and risk factors for PPH.

We find a definitively lack of additional uterotonic need after CS in the Carbetocin receiving women at high risk for PPH. Also, our results suggest the effectiveness of Carbetocin compared to oxytocin regarding the uterine contraction and tonicity.

Reyes OA and Gonzalez GM et al.**,** performed a prospective double-blinded randomized controlled trial in 60 women with severe preeclampsia who were randomized to receive either oxytocin or Carbetocin during the third stage of labor. They found that Carbetocin was as effective as oxytocin in the prevention of PPH. Carbetocin had a safety profile similar to that of oxytocin, and it was not associated with the development of oliguria or hypertension. They concluded that Carbetocin is an appropriate alternative to oxytocin for the prevention of PPH in women with severe preeclampsia **(Reyes & Gonzalez, 2011).**

Uterotonics failed to prevent and control PPH in 20 patients (8 patients in Carbetocin group and twelve patients in oxytocin group) who required further surgical management. In Carbetocin group: eight patients had atonic postpartum hemorrhage which managed surgically by bilateral uterine artery ligation followed by compression sutures. In oxytocin group: twelve patients had atonic postpartum hemorrhage which managed surgically by bilateral uterine artery ligation followed compression sutures, hysterectomy was the final solution for intractable hemorrhage in one of them.

This agree with the fact that Carbetocin has a much longer lasting effect than oxytocin, necessitating only a single dose. Carbetocin inhibits endogenous oxytocin release, interrupting the uterine feedback loop with the hypothalamus and decreasing both central and peripheral release of oxytocin. In comparison with oxytocin, Carbetocin induces a prolonged uterine response when administered postpartum, in terms of both amplitude and frequency of contractions **(Taheripanah et al., 2018)**

Askar and colleagues' performed a study included 240 healthy women with viable normal singleton pregnancies achieving normal vaginal delivery at or beyond 37 weeks' gestation at Al-Azhar University hospital. There was a statistically highly significant difference in the estimated mean blood loss between the carbetocin and syntometrine groups, with a blood loss of 81.5 ml higher in the syntometrine group. The mean drop of hemoglobin concentration 24 h after delivery was 0.8 g/dl in carbetocin group and 1.1 g/dl in syntometrine group, and the difference was statistically highly significant. Women in the carbetocin group were less likely to experience nausea and vomiting**(Askar et al., 2011)** It is not possible to determine whether carbetocin reduces the incidence of PPH following vaginal delivery, possibly because all the studies have been underpowered for this rare outcome.

The results of the current study suggested that carbetocin may be a more potent oxytocic, but it is unclear whether this will reduce the rate of PPH and in particular major PPH. This agree with what demonstrated in previous **(Attilakos et al., 2010; Larciprete et al., 2013)**, but no study of those (including this one) had demonstrated a significant difference in the rate of PPH, which is arguably a more important outcome. The reason for this is that only a very large study with many thousands of women would have adequate power to demonstrate a significant difference in this relatively rare outcome.

Nevertheless, the lower use of additional uterotonic drugs is an important outcome with possible financial savings if the additional oxytocic requires prolonged administration on the labour ward or in the recovery area. However, this may be offset by the higher cost of Carbetocin in comparison to oxytocin. The high use of additional uterotonic drugs (administration of oxytocin for the majority of women) raises the question whether an additional oxytocin infusion should be administered routinely after a caesarean section, given the short half-life of oxytocin. If the oxytocin infusion proves superior to the oxytocin bolus, the next logic step would be to compare Carbetocin with oxytocin bolus followed by oxytocin infusion.

Such a study should include in the outcomes the duration of stay in the Delivery Suite/Recovery area, as this has an impact on the efficiency of busy maternity units.

Conclusion

A single injection of Carbetocin appears to be more effective than a continuous infusion of oxytocin to maintain adequate uterine tone. Further studies are needed to verify our findings.

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