Effect of Carbetocin versus Effect of Oxytocin in Prophylaxis of Postpartum Hemorrhage

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Abstract: Background: Postpartum hemorrhage is the single largest and leading cause of maternal morbidity and mortality not only in developing countries but also in developed countries. **Objective:** Comparison between the effect of carbetocin and oxytocin in the prevention of postpartum hemorrhage. **Patients and Methods:** This study was carried out in El Galaa Teaching Hospital as a randomized controlled trial compared oxytocin agonist (carbetocin). The study included one hundred women who underwent cesarean deliveries for occurrence of atonic postpartum hemorrhage. **Results:** The study showed a highly statistically significant difference between the two groups in favor of the carbetocin before and after regarding hemoglobin and other vital parameters. **Conclusion:** Single injection of carbetocin appeared to be more effective than a continuous infusion of oxytocin to maintain adequate uterine tone and postpartum hemorrhage in the third stage and in the first 24 hours after delivery defined "four stage of labor".

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Key words: Carbetocin, oxytocin, prophylaxis, postpartum hemorrhage.

1. Introduction:

The third stage of labor is the most crucial stage, which begins with expulsion of baby and ends with expulsion of placenta and membranes. Its average duration is 15 min in both primigravida and multigravida ***(Carroli et al., 2008).*** Postpartum hemorrhage (PPH) is one of the dreaded complications of third stage of labor. Every 4 min, a woman dies during childbirth in India ***(Shah et al., 2006).*** Maternal mortality rate in India is 212 per100,000 live births. Among these, 30 % of deaths are due to postpartum hemorrhage ***(Sunil Kumar et al., 2016).***

Postpartum hemorrhage (PPH) is defined as blood loss of more than 500ml following vaginal delivery or more than 1000 ml following cesarean delivery as loss of these amounts within 24 hours of delivery is termed primary PPH, whereas or secondary PPH if they occur 24 hours after delivery ***(Rizvi et al., 2006)***.

Oxytocin is usually given as a first-line agent, and is often already administered prophylactically as part of active management of the third stage of labor. The recommended dose is 10 to 40 units in 1 L of normal saline or lactated Ringer's intravenously at a rate of 125 to 250 mL/h or 10 units intramuscularly (including directly into the myometrium in the setting of a cesarean section). Higher doses of oxytocin (up to 80 units in 1000 mL) can be infused intravenously for a short duration to manage uterine atony**.** Oxytocin generally is well tolerated and has few side effects, but rapid intravenous push may, rarely, contribute to hypotension and lead to cardiovascular collapse ***(Leduc et al., 2009).***

In comparison to oxytocin, carbetocin induces a prolonged uterine response when administered postpartum, in terms of both amplitude and frequency of contractions. The potential advantage of intramuscular carbetocin over intramuscular oxytocin is its longer duration of action. Its relative lack of gastrointestinal and cardiovascular side effects should also prove advantageous compared to Syntometrine and other ergot alkaloids. Carbetocin is currently indicated for prevention of uterine atony after delivery by caesarean section in spinal or epidural anesthesia in 23 countries. However, it is not approved by the FDA for use following vaginal births ***(Attilakos et al., 2010).***

The aim of the present work wastomake a comparison between the effect of carbetocin and oxytocin in the prevention of postpartum hemorrhage.

2. Patients and methods

Technical design:

Randomized controlled trial study compared oxytocin a ganist (carbetocin).

was carried out in **El Galaa Teaching Hospital** included one hundred women with a risk of atonic post partumhaemorrhage and undergo cesareandeliveries for prevention of occurrence of atonic postpartum hemorrhage.

Include the following criteria:

- **Inclusion Criteria**
  - Patient of 20-40 years old

- Multiple Pregnancy
- Hydramnios
- Fetal macrosomia
- Previous post partum haemorrhage
- Prolonged labor

- **Exclusion Criteria**
  - Hypersensitivity to carbetocin or oxytocin
  - Hepatic or renal disease
  - Cases of pre-eclampsia and eclampsia
  - Serious cardiovascular disorders
  - Epilepsy
  - Gestational diabetes mellitus

Randomization:

Women fulfilling the inclusion criteria after history taking were and omized to 2 groups. Randomization was done by using of random table and then odds numbers assigned to carbetocin group and even number to oxytocin group.

Group (1) included 50 women in whom carbetocin given (100 µg) single intravenous does after delivery of the baby and befor delivery of the placenta then observation for the outcomes. ***Group (2)*** included 50 women in whom oxytocin (20 IU) was given as an intravenous infusion after delivery of the baby.

Patients were subjected to full history taking, general, local examinations and laboratory investigations.

- Liver function tests especially liver enzymes mainly aspartate amino transferase (AST) alanie amino transferase (ALT). to exclude hepatic patients.
- Kidney function tests creatinin and uric acid. To exclude renal affiction
- Complete blood picture before and after 24 hours to diagnose anemia blood disorder
- Coagulation profile. PT, PTT, INR

- Weight differenceof cloths used during delivery
- Postoperative bleeding in the first 6 hours calculated by weight difference of pads used.

Post operative follow up:

1. Vital signs (pulse rate ' blood pressure
2. Uterine contractility
3. Need for uterine massage
4. Additional treatment such as oxytocin or ergot alkaloid ingection
5. Occuranc of PPH: loss of blood that affecting general condition
6. Need for blood transfusion
7. Need for surgical intervention such as (uterine artery ligation' Internal iliac artery ligation ' Hystrectomy)

Primary outcome measure:

Need for additional uterotonic intervention in the first 24hours after delivery to maintain the uterus well contracted.

Secondary outcomes:

Maternal:

1. Need for uterine massage
2. Need for blood transfusion
3. Additional treatment for PPH (uterine tamponade – X-ray embolisation
4. Side effects (elevation of blood pressure – vomiting – nausea – shivering – hyperyrexia – headache – chest pain – shortness of breath – diarrhea).
5. Maternal death or severe morbidity (e.g major surgery, organ failure, intensive care unit admission, hyperpyrexia)

Neonatal:

1- Admission to neonatal intensive care unit
2- Respiratory distress
3- Jaundice requiring phototherapy.

3. Results

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Group (1) included 50 women in which carbetocin given (100 µg) single intravenous does after delivery of the baby and before delivery of the placenta then observation for the outcomes.

Group (2) included 50 women in which oxytocin (10 IU) was given as an intravenous infusion after delivery of the baby.

The comparison between carbetocin group and oxytocin group as regard demographic characteristics of the study participants had shown the following results:

4. Discussion

Postpartum haemorrhage (PPH) is the most common complication of third stage of labor. Third stage of labor is always a time of anxiety as the normal case can within a minute become abnormal and successful delivery can turn into a maternal mortality. The most common cause of maternal mortality is PPH which accounts for about 25-30% of maternal mortality ***(Shravage and Silpa, 2007)***. Most of these deaths are due to PPH, resulting from atonic uterus ***(Walraven et al., 2005)***.

The most important risk factors for PPH were related to an abnormal third stage of labor as the duration of third stage of labor more than or equal to 30 min or retained placenta ***(Bais et al., 2006).***

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. Almost 500.000 women die for this potentially preventable cause each year, and up to an estimated quarter of these deaths uses to occur as a consequence of haemorrhage at time of delivery ***(World Health Organisation, 2005)***.

Table (1): Comparison between carbetocin group and oxytocin group

	Groups					
	Oxytocin		**Carbetocin**		**Tests**	
					X^2/t	P-value
Age						
Range	19-40		20-40		1.592	0.115
Mean±SD	31.45±5.87		29.82±4.24			
Gestational age						
Range	37-40		37-40		0.625	0.534
Mean±SD	37.75±2.64		38.06±2.31			
Parity						
0	14	28.0	15	30.0	2.793	0.732
1	8	16.0	12	24.0		
2	11	22.0	6	12.0		
3	5	10.0	4	8.0		
4	6	12.0	5	10.0		
5	6	12.0	8	16.0		
Riskfactors						
Polyhydraminos	8	16.0	7	14.0	0.078	0.779
Large size fetus	6	12.0	5	10.0	0.102	0.749
Diabetes mellitus	7	14.0	6	12.0	0.088	0.766
Multiple gestation	9	18.0	7	14.0	0.298	0.585
Grand multi para	8	16.0	8	16.0	0.000	1.000
Old primigravida	4	8.0	8	16.0	1.515	0.218
Prev. p p hge	8	16.0	9	18.0	0.071	0.790
Post partum hemorrhge						
Yes	2	4.0	3	6.0	0.211	0.646
No	48	96.0	47	94.0		

This table show non statistically significant difference between two groups regarding age, gestational age, parity, risk factors and Post partum hemorrhge when p-value was >0.05.

Table (2): Comparison between both groups as regards before and after administration of the drug

Groups	**Before**	**After**	**Paired t-test**	
			t	**P-value**
wt. of clothes by gm				
Oxytocin	1726.34 ± 357.32	2098.0 ± 267.52	5.888	<0.001*
Carbetocin	1850.52 ± 289.56	2109.0 ± 186.67	5.305	<0.001*
Wt of pads by gm.				
Oxytocin	212.0 ± 37.46	374.5 ± 111.7	9.753	<0.001*
Carbetocin	605.3 ± 41.27	818.0 ± 92.43	14.858	<0.001*
Hemoglobin				
Oxytocin	11.25 ± 1.06	10.57 ± 0.97	3.346	<0.001*
Carbetocin	10.65 ± 0.67	10.32 ± 0.84	2.172	0.032*
Hematocrite				
Oxytocin	33.42 ± 4.25	31.27 ± 2.95	2.939	0.004*
Carbetocin	31.75 ± 3.94	30.74 ± 2.46	1.538	0.127

This table shows highly statistically significant difference between two before and after administration of the drug in two groups regarding wt. of clothes by gm, Wt of pads by gm Hemoglobin and Hematocritewhen p-value was <0.001*.

Non fatal PPH can result in further interventions, severe anaemia, need of blood transfusion, Sheehan's syndrome (pituitary infarction), coagulopathy and organ damage due to hypotension and shock. PPH diagnosis is based on International Classification of Disease (ICD) codes recorded in Perinatal Database (ICD-9 and ICD-10). Subtypes of PPH identified with ICD-9 and ICD-10 diagnostic codes included: PPH due to retained placenta, PPH due to uterine atony (occurring within 24 hours following delivery), delayed and secondary PPH (occurring after the first 24 hours following delivery) and PPH due to a coagulation defects ***(Knight et al., 2009)***.

Knight et al. (2009) reported an increasing trend in coded PPH between 1991 and 2006 not only in low income countries, but also in Canada, New South Wales and the USA, as a possible result of increased maternal age at childbirth, increased rate of caesarean delivery, increased rate of induction of labor and higher number of multiple pregnancies.

The first cause of haemorrhage at the time of delivery is uterine atony, therefore there is general agreement that active management of the third stage of labour rather than expectant management is recommended. The third stage of labor is defined as the period that follows delivery and finishes with the delivery of placenta ***(Su et al., 2007)***.

Leduc et al. (2009) suggested that the active management of the third stage of labour reduces the risk of PPH compared with the expectant management and should be offered and recommended to all women. The administration of uterotonic drugs widely prevents the PPH, significantly decreases the incidence of PPH and therefore it is the main point of active management. Oxytocin (10 IU), administered intra-muscularly, is the preferred medication for the prevention of PPH in low-risk vaginal and caesarean deliveries. Care providers should administer this medication after delivery of the anterior shoulder. Intravenous infusion of oxytocin (20 to 40 IU in 1000 mL, 150 mL/hour) is an acceptable alternative for the active management. Ergonovine can be used but it may be considered a second choice to oxytocin due to the greater risk of maternal adverse effects. Carbetocin, given 100 μg as an IV bolus over 1 minute, instead of continuous oxytocin infusion, can be administered in elective caesarean section for the prevention of PPH, in the attempt to decrease the need for therapeutic uterotonics. Although the oxytocin is the most widely accepted uterotonic agent, however other drugs are available, but which agent is ideal for prophylactic use is far to be clearly stated.

Carbetocin is a long-acting synthetic oxytocin analogue, 1-deamino-1-monocarbo-(2-O-Methyltyrosine)-oxytocin, firstly described in 1987. It has a half-life of 40 minutes (around 4–10 times longer than oxytocin) and uterine contractions occur in less than two minutes after intravenous administration of optimal dosage of 100 μg. A single dose of carbetocin has been hypothysed to act as a 16 hours intravenous oxytocin infusion regarding the increase in uterine tone and the reduction of the risk of PPH in elective caesarean section ***(Boucher et al., 1998)***.

Attilakos et al. (2010) suggested that prophylactic administration of carbetocin may be a good alternative to oxytocin to prevent post-partum haemorrhage, but which uterotonic agent is ideal for prophylactic use is being debated. Nonetheless, primary prevention of a post-partum haemorrhage begins with the assessment of identifiable risk factors.

The women in this study were divided into 2 groups:

1- Carbetocin group included 50 women who had used carbetocin after delivery of the baby and befor delivery of the placenta.

2- Oxytocin group included 50 women who had used oxytocin after delivery of the baby.

In this study, the mean participant's age in oxytocin group was 28.8 ± 6 years and in carbetocin group was 27. 8 ± 6 years. There were no stastically significant differences oxytocin group and carbetocin group regarding age, gravidity and parity ($p > 0.05$).

Also, there wereno statistically significant differences between carbetocin group and oxytocin group as regard risk factors of postpartum hemorrhage, contractility, need of uterine massage, need further uterotonic agent, occurrence of PPH, need for blood transfusion, surgical intervention and adverse effects ($p > 0.05$).

In ***Askar et al. (2011)*** study, women in the carbetocin group had lower incidence of nausea and vomiting, and the difference between the two groups was statistically significant. However, the incidence of other adverse effects such as flushing, headache, and abdominal pain were low and similar for both groups. Also, **Leung et al. (2006)**study has shown that the incidence of nausea and vomiting in the carbetocin group was lower than the oxytocin group.

Moertl et al. (2011) showed that patients treated with oxytocin has a more pronounced hypotension and haemodynamic rebound than patients treated with carbetocin, with comparable effects on the cardiovascular system.

Conclusion

Single injection of carbetocin appeared to be more effective than a continuous infusion of oxytocin to maintain adequate uterine tone and postpartum hemorrhage in the third stage and in the first 24 hours after delivery defined "four stage of labor".

References

1. Askar AA, Ismail MT, El- Ezz AA and Rabie NH (2011): Carbertocin versus syntometrine in the management of third stage of labor. Archives of Gynecology and Obstetrics; 284(6):1359-65.
2. Attilakos G, Psaroudakis D, Ash J, Buchanan R, Winter C, Donald F, Hunt LP andDraycott T (2010): Carbetocin versus oxytocin for the prevention of postpartum haemorrhage following caesarean section: the results of a double-blind randomised trial. BJOG: An International Journal of Obstetrics and Gynaecol; 117 (8): 929–36.
3. Bais JM, Eskes M and Andpel M (2006): Postpartum hemorrhage in nulliparous women: incidence and risk factors in low and high risk women. adutch population – based cohort study on standard > 500ml and severe (>1000ml) postpartum hemorrhage Eur j; 115 (2): 166-72.
4. Begley CM, Gyte GML, Murphy DJ, Devane D, McDonald SJ and McGuire W (2010): Active versus expectant management for woman in the third stage of labour. Cochrane Database of Systematic Reviews; Issue 7.; 113:1459-64.
5. Borruto F, Terisser A, and Comparetto C (2009): Utilization of carbetocin for prevention of postpartum hemorrhage after cesarean section: arandomized clinical trial. Archives of Gynecology and Obstetrics; 280(5): 707-12.
6. Butwick AJ, Coleman L and Cohen SE (2010): Minimum effective bolus dose of oxytocin during elective caesarean delivery. Br J Anaesth; 104:338–343.
7. Cantwell R, Clutton-Brock T, Cooper G, Dawson A, Drife J and Garrod D (2011): Saving mothers lives: reviewing maternal deaths to make motherhood safer: 2006-2008. The eighth report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. BJOG: an international journal of obstetrics and gynaecology; 118(sippl1):1-203.
8. Carroli G, Cuesta C and Abalos E (2008): Epidemiology of postpartum haemorrhage: a systematic review. Best Pract Res Clin Obstet Gynaecol.; 22:999–1012.
9. Carroli G, Cuesta C and Abalos E (2008): Epidemiology of postpartum haemorrhage: a systematic review. Best Pract Res Clin Obstet Gynaecol.; 22:999–1012.
10. De Bonis M, Torricelli M and Leoni L (2012): Carbetocin versus oxytocin after caesarean section: similar efficacy but reduced pain perception in women with high risk of postpartum haemorrhage. The J of Maternal-Fetal and Neonatal Med; 25:732–735.
11. Eskild A, Vatten LJ (2009): Abnormal bleeding associated with preeclampsia: a population study of 315,085 pregnancies. Acta Obstet Gynecol Scand; 88: 154–8.
12. Knight M, Callaghan WM and Berg C (2009): Trends in postpartum hemorrhage in high resource countries: a review and recommendations from the International Postpartum Hemorrhage Collaborative Group. BMC Pregnancy Childbirth; 9: 55.
13. Larciprete G, Montagnoli C and Frigo M (2013): Carbetocin versus oxytocin in caesarean section with high risk of postpartum haemorrhage. J Prenat Med; 7(1): 12-18.
14. Leduc D, Seinkas V and Lalonde AB (2009): SOGC Clinical Practice Guidline, NO 235, Active management of the third stage of labour, prevention and treatment of postpartum hemorrhage. J Obstet Gynaecol Can; 31:980-93.
15. Leung SW, Ng PS, Wong WY and Cheung TH (2006): A randomized trial of caebetocin versus syntometrine in the management of the third stage of labour. BJOG: an international journal of obstetrics and gynaecology; 113:1459-64.
16. Li C, Wang W and Summer SN (2008): Molecular mechanism of antidiuretic effect of oxytocin. J Am Soc Nephrol; 19:225–232.
17. Moertl MG, Friedrich and Krashl J (2011): Haemodynamic effects of carbetocin and oxytcin given as intravenous bolus on women undergoing caesarean delivery: a randomised trial. B J Obstet and Gynaecol; 118:1349–1356.
18. Reyes OA and Gonzalez GM (2011): Carbetocin versus oxytocin for prevention of postpartum hemorrhage in patients with severe preeclampsia: A double-blind randomized controlled trial. J Obstet Gynaecol Can; 33(11): 1099-1104.
19. Rizvi F, Mackey R and Barrett T. (2006): Successful reduction of massive postpartum hemorrhage by use of guidelines and staff education. BJOG; 111(5):495-8.
20. Shah D, Divakar H and Meghal T. (2006): Combating post partumhemor- rhage in India: moving forward. In: Christopher B-L, Louis GK, Andre BL, Mahantesh K, editors. A Textbook of postpartum hemorrhage, a comprehensive guide to evaluate, management and surgical intervention. 1st ed. UK: Sapiens Publishing; 2006. p. 434–41.
21. Shravage JC and Silpa P. (2007): Randomized controlled trial of placental blood drainage for the prevention of postpartum hemorrhage. J Obestet Gynecology India, vol 57, and no.3.
22. Su LL, Ching YS and Samuel M (2012): Carbetocin for preventing post-partum haemorrhage. Cochrane Database Syst Rev; 15: CD005457.
23. Sunil Kumar KS, Shyam Sand Batakurki P. (2016): Carboprost Versus Oxytocin for Active Management of Third Stage of Labor: A Prospective Randomized Control Study. J Obstet Gynaecol India 66: 229-234.
24. Sunil Kumar KS, Shyam S and Batakurki P. (2016): Carboprost Versus Oxytocin for Active Management of Third Stage of Labor: A Prospective Randomized Control Study. J Obstet Gynaecol India 66: 229-234.
25. Walraven G, Blum J and Dampha V (2005): Misoprostol in the management of the third stage of labor in the home delivery setting in rural Gambia: A randomized controlled trial. BJOG; 601-611.
26. World Health Organisation (2008): The World health report 2008: make every mother and child count. Geneva.

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