Research Article

The use of carbetocin versus oxytocin for prevention of postpartum hemorrhage in Minia maternity hospital
(Randomized controlled trial)

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Abstract
Objectives: Evaluation of the prophylactic role of carbetocin versus oxytocin in prevention of the occurrence of PPH in high risk patients. **Patients and Method:** The study included 380 patients pregnant (37–42) weeks gestation having at least one high risk factor for postpartum hemorrhage. Patients were allocated into two groups to receive either 100μg of carbetocin or 20 IU of oxytocin as early as possible after delivery of the anterior shoulder. **Results:** As regards mean blood loss and incidence of PPH; they were lower in women received carbetocin but with no significant difference between the two groups. A significant difference was noticed between the two groups as regards drop in hemoglobin (mean ± SD: 0.53±0.36 vs. 0.69±0.37) (95% CI −0.26 to −6.22, P=0.02), need for additional uterotonics (95% CI 8.33 to 0.36, P=0.002), interventional procedures, blood transfusion (95% CI −9.68 to 0.18, P=0.04) and occurrence of side effects in favor of carbetocin group. **Conclusions:** Carbetocin spares the use of additional uterotonics, interventional procedures & blood transfusion with minimal drug related adverse effects and these results establish carbetocin as a perfect alternative to oxytocin as a prophylactic agent against PPH in high risk patients.
Key words: Postpartum hemorrhage, oxytocin, carbetocin.

Introduction
Postpatrum hemorrhage (PPH) is considered the first cause of maternal mortality in developing world [(1)]. It is estimated that more than 100.000 maternal deaths occurs every year as a result of PPH[(2)]. Uterine atony is the leading cause of PPH accounting for 50% to 60% of cases[(3)]. The incidence of PPH rose from 1.5% in 1999 to 3.4% in 2009 and the incidence of atonic PPH rose from 1% to 3.4% in the same period[(4)].

Active management of the third stage of labor lowers maternal blood loss and reduces the risk of PPH. Prophylactic uterotonic agents should be offered routinely in the management of the third stage of labor in all women as they reduce the risk of PPH by 60%[(5)]. The commonly used uterotonics are oxytocin and syntometrine (a mixture of 5IU oxytocin and 0.5mg ergometrine). This mixture has the advantage of combining the rapid effect of oxytocin and the sustained uterotonic effect of ergometrine. However, the use of syntometrine is associated with cardiovascular and gastrointestinal side effects such as nausea, vomiting and blood pressure rise due to the vasoconstrictor and smooth muscle stimulating effect of ergometrine[(6)]. Prostaglandins such as misoprostol are not as effective as oxytocin but they can be used when the later is not available as in home-birth setting[(7)].

Carbetocin is synthetic long-lasting oxytocin agonist analogue with prolonged half-life[(8)]. It seems to be a promising medication as its prolonged action can offer an advantage over oxytocin in the management of the third stage of labor particularly in patients at risk of PPH[(9)]. The side effect profile of carbetocin was not found to be different from that of oxytocin[(10&11)].

The aim of the current study was to compare the effectiveness and safety profile of single IV bolus dose of carbetocin versus continuous IV infusion of oxytocin in patients at risk of atonic PPH.

Patients and methods
This study is a prospective randomized controlled trial included 380 women attending Minia Matrenity university Hospital. The study was approved by the local ethical committee and all participants gave a signed informed consent before being included in the study.

The study included women pregnant 37 to 42 weeks and have at least one risk factor for PPH. Risk factors included high parity (>5), BMI > 35, history of PPH, antepartum hemorrhage in current pregnancy, anaemia (Hb %< 10.5gm/ dl), Pre-exiting hypertension and over distended uterus (multiple pregnancy and polyhydramnios). Women with coagulopathy and those with known allergy to carbetocin or oxytocin were excluded.

All eligible participants were subjected to through history taking, obstetric ultrasound examination and investigations (complete blood count, coagulation profile renal and liver function tests).

Sample size calculation:
Sample size was calculated to prevent type II error. The average blood loss in cases at risk of PPH in whom oxytocin was used at the hospital where the study was conducted was estimated to be 710 ± 322 ml (figure obtained from the hospital audit report for the year preceding the trial). To be of clinical significance, it was assumed that use of carbetocin should reduce blood loss by 20%. Based on these data, we would need to study 81 patients in each arm to be able to reject the null hypothesis that the rates for study and control groups are equal in intraoperative blood loss at a probability of 80%. The type one error probability associated with this test for the null hypothesis is 0.05. To compensate for patients' withdrawal, we recruited 190 patients in each arm.

Randomization:
Patients were then randomized to receive either 100μg carbetocin diluted in 10 ml of Ringer's lactate solution (Pabal; Ferring, Langley, UK) or two ampoules 20 IU oxytocin (Syntocinon; Alliance, Chippenham, UK) in 1000 ringer lactate as IV drip given intravenously immediately after delivery of the anterior shoulder except in case of twin pregnancy where treatment was given after delivery of the second baby. Slow administration was ensured to reduce the potentially harmful hemodynamic effects of oxytocin and presumably carbetocin. Randomization was done through computer generated random tables.

Outcome measures:
- The primary outcome measures of the study were the estimated blood loss and the hemoglobin deficit defined as the difference between hemoglobin level before and after delivery.
- The secondary outcome measures of the study were the need for additional uterotonics, interventional procedures, blood transfusion and the adverse effects to the treatment.

Statistical methodology:
Data were analyzed using SPSS version 21. Data were described in terms of mean ± standard deviation (SD) for quantitative data and number and frequencies for categorical data. For comparative statistics, Student t-test was used for quantitative and chi-square test for categorical date. A P value of < 0.05 was considered significant.

Results

The study included 380 patients divided into two groups (190 patients in each group). There was no significant difference regarding the patients' characteristics between the two groups as shown in table 1.

Table (1): Characteristics of the study population.

	Carbetocin group (n = 190)	Oxytocin group (n = 190)	P value
Age	28.2 ± 6.9	29.1 ± 6.3	0.38
Parity	4.2 ± 1.5	4.3 ± 1.4	0.74
BMI (kg/m3)	33.6 ± 4.3	32.7 ± 4.2	0.75
Gestational age (weeks)	37.4 ± 1.6	37.3 ± 1.4	0.91
Haemoglobin level (gm/dl)	10.6 ± 1.5	10.8 ± 1.7	0.56
Mode of delivery: **-vaginal delivery** **-Caesarean section**	 57 (30%) 133 (70%)	 50 (26%) 140 (74%)	0.53

Data is presented as mean ± SD or frequency and percentages.

There was no significant difference between the two groups as regards the risk factors for PPH except for placental abruption where there was 19 cases in the carbetocin group as compared to 4 cases in the oxytocin group (P = 0.01) as shown in table 2.

Table (2): Risk factors for PPH in the study population.

	Carbetocin group (n = 190)	Oxytocin group (n = 100)	P value
History of PPH	23 (12%)	19 (10%)	0.65
APH: **- Placenta praevia** **- Placental abruption**	 23 (12%) 19 (10%)	 23 (12%) 4 (2%)	 1 0.01*****
Anaemia	19 (10%)	15 (8%)	0.62
Pre-existing hypertension	30 (16%)	38 (20%)	0.46
Over-distended uterus	34 (18%)	34 (18%)	1
Prolonged labour (in cases delivered vaginally)	19 (10%)	23 (12%)	0.65
BMI > 35	8 (4%)	4 (2%)	0.67

Data is presented as frequency and percentages.

Statistically significant. *

There was no significant difference between the two group as regards the estimated blood loss or the incidence of primary PPH. However, there was significant reduction in hemoglobin deficit in the carbetocin group as compared to the oxytocin group (0.53 ± 0.36 vs.0.69 ± 0.37, P = 0.002). The need for additional uterotonics, further surgical inteventions and blood transfusion were lower in the carbetocin group in comparison with the oxytocin group (38% vs. 60%, P = 0.002; 12% vs. 38%, P = 0.0002; 18% vs. 30%, P= 0.04 respectively). The outcome measures in the two groups are shown in table 3.

Table (3): Outcome measures in the two groups.

	Carbetocin group (n = 190)	Oxytocin group (n = 190)	P value
Estimated blood loss (ml)	535.2 ± 332.9	592.2 ± 341.5	0.23
Primary PPH	38 (20%)	48 (25%)	0.81
Hemoglobin deficit (gm/dl)	0.53 ±0.36	0.69 ± 0.37	0.002*
Additional uterotonics needed	72 (38%)	114 (60%)	0.002*
Further Intervention needed	23 (12%)	72 (38%)	0.0002*
Need for blood transfusion	34 (18%)	57 (30%)	0.04*

Data is presented as mean ± SD or frequency and percentages.
Statistically significant*

Side effects in the two groups were recorded. There were less cases of nausea, vomiting and palpitations in the carbetocin group compared to the oxytocin group (6% vs. 18%, P = 0.009 and 13% vs. 28%, P = 0.008, respectively). On the other hand, there were more cases of flushing in the carbetocin group (6% vs. 2%, P = 0.27). There were no significant differences between the two groups regarding other side. Side effects in the study population are shown in table 4.

Table (4): Side effects recorded in the two groups.

	Carbetocin group (n = 190)	Oxytocin group (n = 190)	P value
Nausea and vomiting	11 (6%)	34 (18%)	0.009*
Shivering	15 (8%)	8 (4%)	0.23
Headache	4 (2%)	4 (2%)	1
Flushing	11 (6%)	4 (2%)	0.27
Palpitations	25 (13%)	53 (28%)	0.008*

Data is presented as frequency and percentages.
Statistically significant*

Discussion

In the current study, the effectiveness and safety of carbetocin were compared with oxytocin in 380 patients with at least one risk factor for PPH. The use of carbetocin was found to be associated with reduction in the need for additional uterotonics, interventional procedures, blood transfusion, a lower drop in hemoglobin level and non-significant reduction in the mean blood loss and incidence of PPH as compared to oxytocin. The side effect profile was in favor of carbetocin.

Attilakos and colleagues conducted a study comparing carbetocin to oxytocin for prevention of PPH in 380 women undergoing cesarean section. In that study, there was no significant difference regarding the estimated blood loss or the hemoglobin deficit. However, 33.5% of women in the carbetocin group required additional uterotonics compared to 44.5% in the oxytocin group (RR = 0.74 (0.57 - 0.95) CI 95%, P = 0.023)[9]. Similar results are reported by Borruto and collegues[12].

On the other hand, the study done by Nirmal and collegues in Malysia on 120 women at risk of PPH failed to find a significant difference in the requirement for additional uterotonics or blood transfusion between carbetocin and oxytocin, However, the hemoglobin deficit was in favor of carbetocin[13].

Regarding the side effect profile, the current study revealed fewer side effects in the carbetocin group compared to the oxytocin group. Similar results are shown by the studied performed by Attilakos et al., (9). No difference in the side effect profile in other studies[13,14].

A recent meta-analysis including 2975 participants form 12 RCT was done to compare the effectiveness and safety of carbetocin and other uterotonic agents in preventing PPH. It was concluded that carbetocin has been associated with a similar low incidence of adverse effects to oxytocin and at least as effective as syntomtrine any may become an alternative uterotonic agent for the prevention of PPH. It was recommended by the authors of this meta-analysis that further studies should be conducted to determine the safety and efficacy profile of carbetocin in women with cardiac disorders and to analyze the cost effectiveness and minimum effective dose of carbetocin[15].

The strengths of the current study are being a RCT and reporting an important clinical outcome with implication on clinical practice. The limitation is the relatively small number included.

In conclusion, carbetocin can be a better alternative to oxytocin in prevention of PPH in at-risk women as in reduces the requirement for additional uterotonics, additional surgical interventions and the need blood transfusion with a better side effect profile compared to oxytocin. Larger studies are needed to confirm this conclusion.

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Conflict of interests:
Authors declare no conflict of interest related to this research.

References

1. Khan KS, Wojdyla D, Say L, et al., WHO analysis of causes of maternal death: a systematic review. Lancet 2006;367:1066–74.
2. Zureick-Brown S, Newby H, Chou D, et al., Understanding Global Trends in Maternal Mortality. Int Perspect Sex Reprod Health. 2013 Mar; 39(1): 10.1363/3903213. doi: 10.1363/3903213
3. Begley CM, Gyte G, Devane D, et al., Active versus expectant management for women in the third stage of labour. Cochrane Database Syst Rev 2011;11: CD007412.
4. Lutomski J, Byrne B, Devane D, Greene R. Increasing trends in atonic postpartum haemorrhage in Ireland: an 11-year population-based cohort study. *BJOG*. Feb 2012; 119(3):306-14.
5. RCOG (2011):Prevention and management of postpartum hemorrhage. RCOG Green-top Guideline No. 52, May 2009Minor revisions November 2009 and April 2011.
6. Carey M. Adverse cardiovascular sequelae of ergometrine. Br J Obstet Gynaecol 1993; 100:865.
7. Tuncalp O, Hofmeyr GJ, Gulmezoglu AM. Prostaglandins for preventing postpartum hemorrhage. Cochrane Database Syst Rev 2012;8:CD000494.
8. Hunter DJ, Schulz P, Wassenaar W. Effect of carbetocin, a long acting oxytocin analog on the postpartum uterus. Clin Pharmacol Ther 1992;52:60–7.
9. Attilakos G, Psaroudakis D, Ash J, et al., Carbetocin versus oxytocin for the prevention of postpartum haemorrhage following caesarean section: the results of a double-blind randomised trial. BJOG 2010; 117:929–36.
10. Leung SW, Ng PS, Wong WY, Cheung TH. A randomised trial of carbetocin versus syntometrine in the management of the third stage of labour. BJOG 2006; 113:1459–64.
11. Moertl MG, Friedrich S, Kraschl J, et al., Haemodynamic effects of carbetocin and oxytocin given as IV bolus on women undergoing CS. BJOG 2011;118(12):1549.
12. Borruto F, Treisser A, Comparetto C. (2009): Utilization of carbetocin for prevention of postpartum hemorrhage after cesarean section: a randomized clinical

trial. Arch Gynecol Obstet2009; 280:707–12.
13. Nirmala K, Zainuddin AA, Ghani NAA, Zulkifli S, Jamil MA.(2009): Carbetocin versus syntometrine in prevention of post-partum hemorrhage following vaginal delivery. J ObstetGynaecol Res 2009; 35: 48–54.
14. El Behery M, El Sayed G, Abd El Hameed et al., Carbetocin versus oxytocin for prevention of postpartum hemorrhage in obese nulliparous women undergoing emergency cesarean delivery, The Journal of Maternal-Fetal & Neonatal Medicine 2015, 29(8), 1257-1260, DOI: 10.3109/ 14767058.2015.1043882
15. Jin B, Du Y, Zhang F at al., Carbetocin for the prevention of postpartum hemorrhage: a systematic review and meta-analysis of randomized controlled trials, The Journal of Maternal-Fetal & Neonatal Medicine 2016, 29(3): 400-407, DOI: 10.3109/ 14767058.2014.1002394