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RESEARCH ARTICLE

CARBETOCIN VERSUS OXYTOCIN FOR MANAGEMENT OF THIRD STAGE OF LABOUR IN WOMEN AT HIGH RISK OF POSTPARTUM HAEMORRHAGE IN A LOW RESOURCE SETTING: A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Aim: To compare the efficacy of carbetocin with oxytocin for prevention of postpartum haemorrhage. **Materials and Methods:** This was a double-blind randomized controlled trial conducted at the Alex Ekwueme Federal University Teaching Hospital Abakaliki, Southeast, Nigeria between 3rd January 2018 to 31st December 2018. One hundred parturients at high risk of postpartum haemorrhage following vaginal delivery were randomly assigned to receive either intramuscular carbetocin 100µg or oxytocin 10IU within one minute after delivery of the baby. The data analysis was performed using SPSS version 22. **Results**: The need for additional uterotonics was significantly lower in carbetocin group when compared with oxytocin group (18% versus 44%, RR = 0.4, 95%CI = 0.21-0.79, P-value = 0.008). The estimated blood loss > 500 ml was significantly higher among study participants that received oxytocin (18% versus 40%, RR = 0.4, 95%CI = 0.20-0.80, P-value = 0.009). Even though that the blood loss > 1000 ml was lower in the carbetocin arm of the study, this difference did not reach statistical significance (8% versus 18%, RR = 0.4, 95%CI = 0.15-1.35, P-value = 0.15). **Conclusion:** Carbetocin reduces the use of additional uterotonics following vaginal delivery in women at high risk of PPH when compared to standard dose of oxytocin. It also reduced the incidence of PPH in these women.

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INTRODUCTION

Postpartum haemorrhage (PPH) is the leading cause of maternal mortality in low-income countries, contributing to nearly a quarter of maternal deaths globally and about 23% of all maternal deaths between January 1999 and December 2008 were estimated to be due to obstetric haemorrhage in a study done in a University Teaching Hospital at Abakaliki, Nigeria (Voon *et al.,* 2018; Ezegwui *et al.,* 2013). The majority of deaths due to PPH could be avoided through the use of prophylactic uterotonics during the third stage of labour and by timely and appropriate management (Larciprete *et al.,* 2013; Begum *et al.,* 2015; Mannaerts *et al.,* 2018; Anandakrishnan *et al.,* 2013; Widmer *et al.,* 2016; Su *et al.,* 2012; Sobkowski *et al.,* 2016; Attilakos *et al.,* 2010; Voon *et al.,* 2018; Reyes, 2011; Widmer *et al.,* 2018; Maged *et al.,* 2016; Rosales-Ortiz *et al.,* 2014; El Behery *et al.,* 2016; Higgins *et al.,* 2011; Borruto, 2009; Boucher, 2004). Injectable oxytocin has been recommended by the World Health Organization (WHO) for routine use during the third stage of labour and is the preferred drug for the prevention and management of blood loss after childbirth; however, several studies have demonstrated that oxytocin loses potency in field conditions, particularly in tropical climates (Mannaerts *et al.,* 2018; Anandakrishnan, 2013). To decrease potency loss due to degradation, oxytocin must be either stored at controlled room temperature (25 °C or lower) for a restricted amount of time or refrigerated (2 °C to 8 °C), making its use difficult in low resource settings where electricity supply is erratic or non-existent (Su *et al.,* 2012). To ease this barrier, several groups have been researching heat stable oxytocin formulations. Though some progress has been made in this area, there is currently no heat stable oxytocin formulation for therapeutic use. Carbetocin (1-deamino-1-carba-2-tyrosine (0-methyl)-oxytocin) is an oxytocin derivative that binds to the oxytocin receptor in the myometrium (Widmer *et al.,* 2016; Su *et al.,* 2012; Sobkowski *et al.,* 2016; Attilakos *et al.,* 2010; Voon *et al.,* 2018; Reyes, 2011; Widmer *et al.,* 2018; Maged *et al.,* 2016; Rosales-Ortiz *et al.,* 2014; El Behery *et al.,* 2016; Higgins *et al.,* 2011; Borruto, 2009; Boucher, 2004). The clinical and pharmacological properties of carbetocin are similar to those of oxytocin. However, carbetocin is a more stable at room temperature and its half-life

of elimination is approximately 40 min after intravenous injection, which is 4 to 10 times longer than that of oxytocin (Sobkowski, 2016). This accounts for its protracted uterotonic activity providing the advantage of a single bolus dosing rather than a continuous infusion as with oxytocin (Attilakos *et al.,* 2010). Heat-stable carbetocin, does not require cold-chain transport and storage; it has been shown to maintain stability over a period of 36 months at 30°C and 75% relative humidity (Widmer, 2018). A room temperature stable (RTS) carbetocin is currently approved in multiple countries for the prevention of PPH during caesarean section (Maged *et al.,* 2016). The drug is licensed to be administered by slow intravenous (IV) single injection at a dose of 100 µg. Carbetocin RTS therefore represents a promising intervention for reducing PPH, particularly in settings where cold storage is difficult to achieve and maintain (Maged, 2016). The aim of this study was to compare the effectiveness of carbetocin with that of oxytocin for prevention of postpartum haemorrhage in high risk women undergoing vaginal delivery.

MATERIALS AND METHODS

This double-blind, randomized, controlled trial was conducted at Alex Ekwueme Federal University Teaching Hospital, Abakaliki, Southeast, Nigeria from 3rd January 2018 to 31st December 2018, after approval of the study by hospital ethical committee. Pregnant women who had at least one risk factor for PPH and who were to undergo vaginal delivery were eligible for inclusion in the study after obtaining informed consent. The risk factors considered were hypertensive disorders in pregnancy, augmentation of labour, induction of labour, chorioamnionitis, abruptio placentae, polyhydramnious, multiparity (>4), previous postpartum haemorrhage, coexisting fibroids, fetal macrosomia, multiple gestation, and one previous caesarean section. The exclusion criteria for the study were history of cardiac, renal and liver diseases, and known allergy to women with no allergies to carbetocin or oxytocin. The care provider in charge of antenatal care at the hospital informed potentially eligible pregnant women about the trial. At admission for labour at the hospital, the women were approached for participation in the trial when they were in early labour. Informed consent was obtained at admission. One hundred women participated in the study. Randomization was performed using computer-generated random numbers in 1:1 ratio. Eligible women were randomly assigned to receive either cabetocin or oxytocin. Patients and investigators were masked to group allocation. According to group assignment, participants received either carbetocin RTS administered as a single IM dose of 100 µg in a 1 mL solution or oxytocin 10 IU/mL administered as a single intramuscular (IM) dose in a 1 mL solution within one minute after the birth of the baby. In order to maintain the blindness of the trial, carbetocin RTS and oxytocin were provided in 1 mL ampoules in consecutively numbered treatment packs arranged in dispensers and stored in a refrigerator at 2 °C to 8 °C. Once the drugs were administered, the birth attendant followed the management of the third stage of labour as recommended in WHO guidelines. Once the umbilical cord was clamped and cut, an impermeable leather drape for blood collection was placed under the woman's buttocks. Blood was collected for 2 hours. The drape with the blood was then weighed by a digital scale, with the weight recorded in grams and then converted to volume (milliliters) after the weight of the drape was subtracted. Additional uterotonic drugs at any time in case of increased vaginal bleeding were administered. In the events of postpartum haemorrhage, treatment according to the postpartum haemorrhage protocol was instituted. Women were followed up to discharge from the hospital.

Outcome measures: Primary outcome measure was the need for additional uterotonics within 24 hours of delivery while the secondary outcome measures were estimated blood loss >500 ml, blood loss > 1000 ml, and blood transfusion requirement.

Sample size calculation: Sample size was calculated using data from previous study (Attilakos *et al.,* 2010) that showed the need for additional oxytocic was 33.5% in women who received cabetocin, in contrast to 45.5% in women who were given oxytocin, and EpiInfo version 7.0, setting the power at 90%, the two-sided confidence level at 95% and 10% patients drop rate. Calculation according to these values, the number of women needed to produce a statistically acceptable figure was 50 in each group. Therefore, one hundred (100) women were recruited for the study.

Statistical analysis: Data were collected, tabulated then statistically analysed by intention-to-treat using the Statistical Package for Social Sciences (SPSS) computer software version 22. Numerical variables were presented as mean±standard deviation (SD), while categorical variables were presented as number and percentage. Relative risk (RR) was used for comparison between groups as regard qualitative variables. Student t-test was used for comparison between groups as regard quantitative variables. A difference with a P value <0.05 was considered statistically significant.

RESULTS

The two studied groups were matched with no significant difference between the carbetocin and oxytocin groups regarding mean age, body mass index (BMI) and gestational age (Table 1), and risk factors for postpartum haemorrhage (Table 2). The need for additional uterotonics was significantly lower in carbetocin group when compared with oxytocin group (18% versus 44%, RR = 0.4, 95%CI = 0.21-0.79, P-value = 0.008) (Table 3). More women needed oxytocin infusion to maintain uterine tone in oxytocin arm of the study. The estimated blood loss > 500 ml was significantly higher among study participants that received oxytocin (18% versus 40%, RR = 0.4, 95%CI = 0.20-0.80, P-value = 0.009). Even though that the blood loss > 1000 ml was lower in the carbetocin arm of the study, this difference did not reach statistical significance (8% versus 18%, RR = 0.4, 95%CI = 0.15-1.35, P-value = 0.15)(Table 3). There was no statistical difference in blood transfusion requirements in both arm of the study (4% versus 10%, RR = 0.4, 95%CI = 0.81-1.97, P-value = 0.26) (Table 3).

DISCUSSION

In this double-blind randomized controlled trial we found that 100 µg intramuscular carbetocin is more effective when compared to standard dose oxytocin for prevention of primary postpartum haemorrhage in high risk women undergoing vaginal delivery. The results demonstrate an increased use of additional oxytocics in the oxytocin arm. Most of the women who were given additional oxytocics received additional oxytocin bolus or infusion. Almost one in two women in the oxytocin arm received an additional oxytocin infusion, which was typically given over 3 hours. The reason for administering additional oxytocics in the oxytocin group was for PPH treatment.

Table 1. Demographic comparison of two group

Variable	Carbetocin (n=50)	Oxytocin (n=50)	P-value
Age(years)	27.2±5.1	27.4±5.2	0.41
Parity	2.0±1.2	1.9±1.3	0.53
BMI(kg/m^2)	24±1.4	25±1.6	0.24
Gestational age(weeks)	38±1.3	39±1.1	0.88

Table 2. Risk factors for Postpartum Haemorrhage

Variables	Carbetocin n=50(%)	Oxytocin n=50(%)	P-value
Hypertension in pregnancy	12(24)	10(20)	0.63
Induction of labour	6(12)	5(10)	0.75
Oxytocin augmentation	8(16)	10(20)	0.60
Chorioamnionitis	1(2)	0(0)	0.49
Abruptio placentae	2(4)	3(6)	0.65
Polyhydramnious	1(2)	2(4)	0.57
Fibriods coexisting in pregnancy	6(12)	4(8)	0.51
Multiparity (≥5)	10(20)	12(24)	0.63
Fetal macrosomia	2(4)	1(2)	0.56
Previous postpartum haemorrhage	2(4)	3(6)	0.65

Table 3. Clinical outcome

Outcomes	Carbetocin n=50(%)	Oxytocin n=50(%)	RR(95% CI)	P-value
Additional uterotonics	9(18)	22(44)	0.4(0.21-0.79)	0.008
Estimated blood loss > 500 ml	9(18)	20(40)	0.4(0.20-0.80)	0.009
Blood loss > 1000 ml	4(8)	9(18)	0.4(0.15-1.35)	0.15
Required transfusion	2(4)	5(10)	0.4(0.81-1.97)	0.26

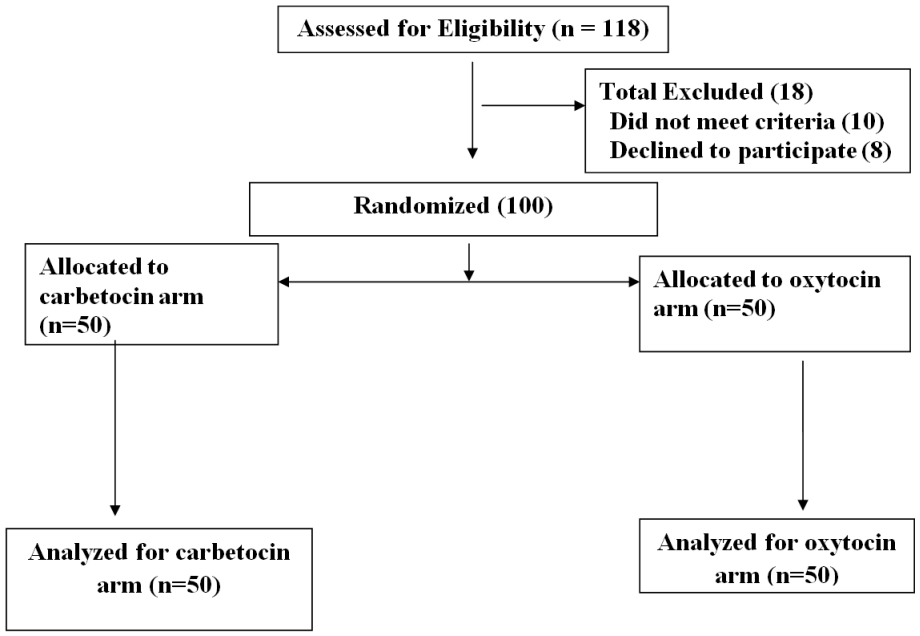

Figure 1. The figure shows the flow of patients through the study

The results suggest that carbetocin is a more potent oxytocic and can reduce the rate of PPH and in particular major PPH. This finding correlates with the result of the recent WHO Carbetocin Haemorrhage Prevention (CHAMPION) Trial Group which showed that intramuscular administration of 100 µg of heat-stable carbetocin was noninferior to 10 IU of oxytocin for the prevention of postpartum hemorrhage and major PPH after vaginal birth, when the outcome was defined as blood loss of at least 500 ml or at least 1000 ml respectively or the use of additional uterotonic agents (Widmer *et al.,* 2018). Other studies also reported similar findings (Maged, 2014; Rosales-Ortiz, 2014; El Behery, 2016; Higgins, 2011; Borruto, 2009; Boucher, 2004).

The result of our study is significant in low resource setting like Nigeria where electricity supply is variable, erratic or nonexistent in rural areas where majority of women reside. Carbetocin has significant advantage in the tropical settings of developing countries by avoiding the need for a cold chain which will enable lower cost transport and storage as well as reduce the waste associated with heat-exposure–related degradation and loss of active ingredient. Within the labour-ward environment, eliminating a need for cold storage will facilitate easier access to the drug for patient care. The lower use of additional oxytocics is an important outcome with possible financial savings if the additional oxytocics require prolonged administration in the labour ward.

The use of carbetocin may lower the cost of health care in our setting where majority of our women are of low socioeconomic status and where payment for health care is made out of pocket. However, this may be offset by the higher cost of carbetocin in comparison to oxytocin which most of women may not afford. There is a need for governments and nongovernmental organization to subsidize this important life-saving drug so as to reduce maternal mortality in our setting. This limitations of this study is that it did not compare the side effects profile and cost effectiveness of carbetocin and oxytocin.

Conclusion

In conclusion carbetocin reduces the use of additional uterotonics following vaginal delivery in women at high risk of PPH when compared to standard dose of oxytocin. It also reduced the incidence of PPH in these women.

Conflict of interest: The authors declare that they have no competing interests.

Author's contribution

Nwafor JI contributed to the design of the study, collection, analysis, and interpretation of the data, and writing the manuscript. Ibo CC contributed to the design of the study, collection and interpretation of the data, and revising the manuscript. Obi CN and Ugoji DC contributed to the design of the study, interpretation of the data, and revising the manuscript. Onwe B contributed to the interpretation of the data and revising the manuscript. Onuchukwu VO contributed to the design of the study, analysis and interpretation of the data, and revising the manuscript. All authors approved publication of the article.

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