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Carbetocin Use during Caesarean Deliveries in Preventing Postpartum Haemorrhage (PPH) In Enugu: A 15-Case Series and Review of Literature

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ABSTRACT

Background: The news of pregnancy is usually a happy one in a family and the birth of a new baby marks the peak of the experience. However, many times this happy beginning is clouded by pain and sorrow when serious maternal morbidity or mortality occurs. The major cause of maternal death is Primary postpartum haemorrhage. The introduction of active management of the third stage of labour has significantly reduced the incidence of maternal mortality but the risk of PPH is not entirely eliminated, hence, the need for a near ideal uterotonic agent that will better prevent or control PPH. Carbetocin promises to be a veritable tool in this regard and this case series was designed to showcase our experience with the drug.

Aim: The aim was to analyze our experiences with Carbetocin during caesarean section in preventing PPH.

Methodology: This was a case series of 15 women who had caesarean delivery in 3 different hospitals in Enugu under cover of Carbetocin. An extensive literature search was also done to unravel the extent of use and reported efficacy or otherwise of Carbetocin compared with our own experience. Relevant data was collated using a proforma and the result was analyzed using SPSS version 25.0

Results: The result from the study showed that out of the fifteen subjects analyzed, 5(33.3%) were less than 30 years while 10(66.7%) were more than 30 years and that 14(93.3%) of them were Igbo, whereas only 1(6.7%) was Yoruba. Seven of them (46.7%) were primipara, 1(6.7%) was para-4 or more and the rest were either between para-2 or para-3. Intra-operatively 12(80%) had no uterine fibroid and 3(20%) had one or more uterine fibroids. It also revealed that 6(40%) were delivered at a gestational age of 38 weeks, 3(20%) at 37 weeks and 1(6.7%) each at 35 weeks and 40 weeks. Only 1(6.7%) had need for additional uterotonics whereas the remaining 14(93.3%) had no need for additional uterotonics during and after the surgery. There was no record of any side-effects in any of the subjects. Prolonged labour and placenta previa with previous caesarean delivery topped the list of indications each having 3(20%) whereas breech presentation and previous caesarean deliveries were 2(13.3%) each; the others constituted the remaining 5(33.3%) each. The mean estimated blood loss was 335.33ml±140.80 (p-value= 0.001 and CI= 4.68-8.26), the average pre-operative packed cell volume (PCV), 34.2%±2.73 whereas the mean post-operative PCV was 30.93%±2.21(p-value = 0.001 and CI= 2.55-3.90). There were no side-effects recorded in any of the subjects.

Conclusion: Carbetocin is an efficacious uterotonic agent and is very effective in preventing uterine atony and PPH during caesarean deliveries with minimal and tolerable side-effects.

KEY WORDS: Carbetocin, Preventing, PPH, Caesarean deliveries, Case-Series

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INTRODUCTION

Primary postpartum haemorrhage (PPH) is one of the most feared complications in pregnancy and a leading cause of maternal mortality globally with an incidence of 2-11%.[1-3] It is defined as the loss of blood from the genital tract of up to 500ml following vaginal delivery or 1000ml following

caesarean delivery or any amount of blood loss that could lead to a woman's cardiovascular instability or reduction of haemoglobin by 10% or more from the baseline within the first 24 hours after delivery.[4-6]It is estimated that globally about 14 million women experience PPH and 70,000 maternal deaths arise from it yearly.[7]It is also known that about 70 to 80% of PPH are caused by uterine atony.[8-11]Therefore, preventing uterine atony especially among women undergoing caesarean delivery and other high risk pregnant women will go a long way in reducing maternal morbidity and mortality arising from PPH.

Over the years, and across generations, history is filled with various attempts by birth attendants and accoucheurs to enhance uterine tone postpartum and reduce the risk of PPH. The first drugs to be used for their uterotonic properties were ergot-alkaloids, followed by oxytocin and at last the prostaglandins.[12]**T**he ergot alkaloids have a lot of side-effects and complications that have limited their use. The active management of the third stage of labour using oxytocin has reduced the occurrence of PPH by 60-70%.[13]In the present day obstetrics the use of oxytocin is firmly established but it appears that the maximum possibilities of the drug have been reached, hence, the need for a more effective uterotonic drug that can meet the need of uterine tone especially among women with high risk pregnancies for PPH such as those undergoing cesarean deliveries.

Carbetocin is a long-acting synthetic oxytocin analogue: 1-deamino-1-monocarbo-(2-O-Methyltyrosine)-oxytocin, first described in 1987 with a half-life of 40 minutes (around 4-10 minutes) longer than oxytocin; and uterine contraction occurs in less than 2 minutes after intravenous administration of optimal dose of 100µg.[14]It is a medication used for preventing PPH after childbirth especially following caesarean section and appears to work as well as oxytocin.[15]It works as an oxytocic, antihaemorrhagic and uterotonic drug and functions as an agonist at peripheral oxytocin receptors, particularly in the myometrium with less affinity for myoepithelial cells. Unlike oxytocin, it does not require constant refrigeration and a cold chain system of storage.[16]This makes it suitable in the resource-poor countries where electricity may not be sufficiently available. The oxytocin receptors are G-protein coupled and the mechanism of action involves second messengers and production of inositol phosphates.[17]It can be administered intravenously or intramuscularly and the recommended dose in an adult is 100µg.

Carbetocin is essentially safe but some minor side-effects have been reported such as nausea, vomiting, abdominal pain, itching, increased body temperature trembling and weakness.[18]Others include back and chest pain, dizziness, chills, sweating, tachycardia and respiratory distress.

The average blood loss during caesarean section is estimated at about 500-600ml by various investigators[19,20] and some recorded even higher values. A systemic review and meta-analysis in 2022 concluded that for patients undergoing caesarean section and vaginal delivery, Carbetocin was superior to oxytocin in effectiveness and similar in safety and therefore recommended Carbetocin as an alternative for oxytocin in preventing PPH.[21]An analysis of the cost-effectiveness of Carbetocin versus oxytocin in the UK concluded that Carbetocin utilization leads to lower prophylactic treatment cost and less PPH events versus oxytocin when utilized for the prevention of PPH following vaginal birth.[22]It was also found that prophylactic single dose of Carbetocin use reduces the need for additional uterotonic agents when compared with standard dose of oxytocin, also reduced the incidence of PPH[23]and similar results were gotten when compared with a combination of oxytocin and ergometrine and fewer side-effects were also observed.[24]However, only 100µg of Carbetocin (a 1 dose fits all preparation) is available despite the differences in body/mass indices and hence, the anticipated weights of our prospective parturient. A smaller dose formulation to meet the need of smaller women may reduce the cost per ample and further make the drug pocket friendly, increase availability and uptake in resource poor countries. This area needs further studies especially in low resource countries like ours. The above findings showed that a lot of works have been done on Carbetocin lately and the need to present our experiences with this novel drug that promises a lot of comparative advantage over the existing uterotonics.

AIM

The aim was to analyze our experiences with Carbetocin during caesarean section in preventing PPH.

OBJECTIVES

The objectives were to determine the:

1. Average estimated blood loss following the use of Carbetocin
2. Average reduction in PCV
3. The proportion that had need for additional uterotonics
4. The common side-effects associated with Carbetocin use during caesarean section in our centres

Study setting/Area: The study was carried out at 3 different centres in Enugu metropolis, the capital of Enugu state South-East, Nigeria. The centres were: Enugu State University Teaching Hospital, SEMINO Specialist Hospital, and Freedom Fertility Centre & Maternity**.**

METHODOLOGY

This was a case series of 15 patients who had caesarean delivery in one of the above listed centres. Most of these women had a high risk for PPH. High risk pregnancy in this study refers to pregnancies with increased tendencies to bleeding after delivery such as placenta praevia, placental abruption, multiple gestation, macrosomia, previous

caesarean deliveries, prolonged labour, grand multiparous women, previous PPH etc.

The enrollees were selected and counseled on the drug and their consent obtained. They were also informed that should bleeding occur, they will be treated in accordance to standard PPH management globally. The pre-operative PCV was done and the values noted. All the surgeries were under spinal anaesthesia after preloading with at least 1 litre of normal saline. After the delivery of the baby 100µg of the **PABAL®** brand of Carbetocin injection was given intravenously and the placenta delivered. The intra-operative blood loss was visually estimated by the obstetrician and the anaesthetist, the average was determined and the value documented. A repeat PCV was done on the 2nd day post-operatively and the values noted. In a situation where the single dose of Carbetocin could not control the bleeding other uterotonics such as oxytocin, prostaglandins and ergot-alkaloids were used to control the bleeding. Any observed side-effects were noted, treated and documented

DATA ANALYSIS

Data was collated using a proforma and analyzed with Statistical Package for Social Sciences, SPSS version 25.0 for Windows. Frequencies, means and percentages were calculated and represented in tables.

RESULTS

The result showed that 15 subjects were involved in the study. **Table 1** below revealed the socio-demographic distribution of the subjects. Out of the fifteen subjects analyzed, 5(33.3%) were less than 30 years while 10(66.7%) were more than 30 years. Majority of them were Igbo 14(93.3%) whereas only 1(6.7%) was Yoruba

Table 1: Sociodemographic distribution

Variable	Frequency	Percentage
Age in years		
<30 years	5	33.3
>30 years	10	66.7
Ethnicity		
Igbo	14	93.3
Yoruba	1	6.7

Table 2 below showed some clinical characteristics of the subjects. Seven of them (46.7%) were primipara whereas 1(6.7%) was para 4 or more and 7(46.7%) were either para-2 or para-3. Intra-operatively 12(80%) had no uterine fibroid and 3(20%) had uterine fibroid of different sizes and numbers. It also revealed that 6(40%) were delivered at a gestational age of 38 weeks, 3(20%) at 37 weeks and 1(6.7%) each at 35 and 40 weeks. Only 1(6.7%) had need for additional uterotonics whereas the remaining 14(93.3%) had no need for additional uterotonics during and after the surgery. There was no record of any side-effects in any of the subjects.

Table 2: Clinical characteristics of the subjects

Variable	**Frequency**	**Percentage**
Parity		
1	7	46.7
2	4	26.7
3	3	20
≥4	1	6.7
Presence of Fibroid		
No	12	80
Yes	3	20
GA @ delivery		
35	1	6.7
37	3	20
38	6	40
40	1	6.7
41	4	26.7

Additional Uterotonics		
No	14	93.3
Yes	1	6.7
Presence of side-effects		
No	14	100

Table 3 below showed the distribution based on the different indications for the surgery. Prolonged labour and placenta previa with previous caesarean delivery topped the list with each having 3(20%) whereas breech presentation and previous caesarean deliveries were 2(13.3%) each; the others constituted the remaining 5(33.3%)

Table 3: Indication for CS

Variable	Frequency	Percentage
Indication for CS		
Breech	2	13.3
Failed Induction	1	6.7
Fetal distress	1	6.7
Previa	1	6.7
Previa and previous CS	3	20
Previous CS	2	13.3
Prolonged Labour	3	20
Triplet gestation	1	6.7
Twin gestation	1	6.7

Table 4 below showed the distribution based on the amount of estimated blood loss (EBL). The mean EBL was 335.33ml±140.80 with p-value of 0.001 and confidence interval of 4.68-8.26, the average pre-operative packed cell volume (PCV), 34.2%±2.73 whereas the mean post-operative PCV was 30.93%±2.21 with p-value of 0.001 and confidence interval of 2.55-3.90

Table 4: Estimated blood loss

Variable	Mean	SD	T test	C.I (95%)
Estimated blood loss	335.33	140.80	4.58 (0.001) *	4.68-8.26
Pre-op PCV	34.2	2.73	9.88(0.001) *	2.55-3.9
Post-op PCV	30.93	2.21		
PCV reduction	3.27	1.28	1	6

DISCUSSION

The aim of this15-case series was to analyze our experiences during caesarean section with Carbetocin in preventing PPH following caesarean deliveries in our centres. It is thought that Carbetocin, a long-acting oxytocin analogue promises to be of better effect in maintaining uterine tone and reducing PPH arising from uterine atony. The estimated mean blood loss from the study was 335.33ml±140.80. This was significantly lower than the average estimated blood loss during caesarean deliveries pegged at 500-600ml by Abdulrahim G et al and Khan FA et al.[19,20] While Abdulkarim and his team worked on 97 full-term pregnant women and compared different methods of estimating blood loss to arrive at their value under standard uterotonic agents, ours was a simple case-series of just 15 women who had cesarean deliveries under Carbetocin and we used only visual estimation to arrive at our value. These variables might have contributed to the differences in the amount of blood loss. On the other hand, Khan et al worked on 126 patients who had caesarean delivery under standard oxytocic agent. The estimation of blood loss also was via different methods including visual by both the anaesthetist and the obstetrician, intra-operative and post-operative transfusion and pre- and post-operative haemoglobin and haematocrit whereas our study was a case-series of 15 subjects under Carbetocin using only one method of estimation(visual method) these differences could also have accounted for the differences. However, one outstanding difference between the quoted studies above and ours is the type of uterotonic agent used.

The mean reduction in the PCV in our study was found to be 3.27±1.28. This differed from the finding of Singh B et al who found an average haematocrit drop of 5.49±1.27 under standard uterotonic cover in a tertiary hospital setting.[25]This difference in the PCV above could be due to the fact that theirs was a prospective, observational study unlike ours and their sample size of 121 was way higher than our sample size of 15. Secondly, this difference may be due to the difference in the choice of uterotonic agents used.

Only 1(6.7%) patient was found to have need for additional uterotonic agent after the use of Carbetocin in our study. This was similar to the finding by Giovanni L et al in 2013 where they found that 23% of women who received oxytocin needed additional uterotonic agent as against 0% among women who had Carbetocin treatment following caesarean section.[26]This was a randomized trial as against our study that was a case-series, yet with similar result. In another study comparing oxytocin and Carbetocin, 216(31.1%) who received oxytocin had need for additional uterotonic agent compared with 88(19.2%) who received Carbetocin.[27]While the above study was a randomized trial involving a large sample size as opposed to our small sample size case-series, both findings still showed that the use of Carbetocin during caesarean section produced better uterine tone and might be better than oxytocin. Another randomized trial still revealed a lower requirement for uterotonic agent following the use of Carbetocin compared with oxytocin (18.4% vs 24.4%) which is more or less the standard care,[28]and this is still in keeping with our finding.

There were no side-effects observed in our series. This may be due to the small number of subjects studied. However, Carbetocin is known to cause some side-effects such as hypotension, fluid over load, nausea, vomiting, etc just like oxytocin.[18]

Most of these studies are in keeping with the findings of a 2022 systematic review and meta-analysis which concluded that for patients undergoing caesarean section and vaginal delivery, Carbetocin was superior to oxytocin in effectiveness and similar in safety, and therefore, recommended Carbetocin as an alternative for oxytocin in preventing PPH.[21]

CONCLUSION: Carbetocin is an efficacious uterotonic agent and is very effective in preventing uterine atony and PPH during caesarean deliveries with minimal and tolerable side-effects.

RECOMMENDATIONS:

1. We recommend a wide-spread use of Carbetocin for prevention of PPH during caesarean sections.
2. We also recommend a more elaborate study to further elucidate the cost-effectiveness or otherwise of Carbetocin.
3. Finally, further studies are recommended to find the relationship between maternal weight and appropriate Carbetocin dose. Instead of the current one-dose-fits-all regimen.

Declaration of conflict of interest: In the course of this study, we did not have any conflict of interest.

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