OPEN ACCESS

Scholars International Journal of Obstetrics and Gynecology

Abbreviated Key Title: Sch Int J Obstet Gynec
ISSN 2616-8235 (Print) |ISSN 2617-3492 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

Original Research Article

The Adverse Effects of Carbetocin Administration in the Third Stage of Labor

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DOI: 10.36348/sijog.2023.v06i08.005 | **Received:** 14.07.2023 | **Accepted:** 21.08.2023 | **Published:** 28.08.2023

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Abstract

Introduction: The pharmacologic agents currently used routinely to prevent postpartum hemorrhage are mainly oxytocin, syntometrine (a combination of oxytocin and ergometrine), and carbetocin. Syntometrine is associated with a statistically significant reduction in the risk of postpartum hemorrhage when compared with oxytocin alone. So, this study aimed to assess the adverse effects of carbetocin administration in the third stage of labor. This study aimed to analyze the adverse effects of carbetocin administration in the third stage of labor. ***Methods:*** This cross-sectional observational study was conducted at the Department of Obstetrics and Gynaecology, Shaheed Suhrawardy Medical College Hospital, Dhaka, Bangladesh. The study period was from May 2016 to October 2016. 100 women undergoing normal vaginal delivery were the study subject. A convenient sampling technique was used in this study. Necessary data was collected in the data collection sheet. Women received a bolus of 100 microgram carbetocin IV at delivery of the anterior shoulder. A standardized deliver mat (Quaiyum's mat) was used before placental removal for measuring blood loss. Statistical analysis was carried out by using the Statistical Package for Social Sciences version 19.0 for Windows (SPSS Inc., Chicago, Illinois, USA). The mean values were calculated by frequencies and percentages. ***Result:*** In this study, the majority (54, 54.0%) of patients belonged to age 20-25 years, followed by (30, 30.0%) >25 years. It was observed that the majority 93(93.0%) patients had regular menstrual history. Concerning the clinical indices, anaemia was found 69(69.0%), jaundice 08(8.0%) and edema 24(24.0%). Additional uterotonices was used in 15(15.0%) and blood transfusion 07(7.0%) patients. Mean blood loss before the use of the weight of Q-mat was found 74.81±1.23 gram, mean blood loss after the use of the weight of Q-mat was 246.28±99.98 gram, and mean net blood loss was 141.61±59.93 gram. Majority 61(61.0%) babies had birth weight ≥2.5 kg. Majority 68(68.0%) patients had Hb% <10.5. The mean Hb% before delivery was 10.3±0.47 gm/dl with a range from 9.40 to 11.20 gm/dl The mean birth weight was found 2.57±0.41 kg with a range from 2.3 to 3.10 kg. ***Conclusion:*** Carbetocin appears to be an effective new drug in the active management of third-stage labor. Carbetocin has associated with a lower risk of various adverse effects and preventing postpartum hemorrhage in women undergoing vaginal delivery.

Keywords: Carbetocin, Vaginal Delivery, Hemorrhage, Anemia.

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INTRODUCTION

Postpartum hemorrhage (PPH) constitutes a major cause of maternal morbidity and mortality [1]. Currently, oxytocin is most frequently used as an agent of first choice after cesarean section. Due to its short half-life (4 to 10 minutes), it requires continuous or frequently repeated administration. More recently carbetocin has been developed as a long-acting oxytocin agonist and when administered it results in a sustained uterine contraction. In a systematic review and meta-analysis of randomized controlled trials, carbetocin is associated with a reduced need for additional uterotonic agents, but no differences are noted for PPH, severe PPH, mean estimated blood loss, or adverse effects [2]. Since carbetocin is a modified version of oxytocin, it should be expected that possible side effects might be similar. Hypotension, an important

hemodynamic side-effect, has been described using both oxytocin and carbetocin [3, 4]. It combines the safety and tolerability profile of oxytocin with the sustained uterotonic activity of injectable ergot alkaloids [5]. Carbetocin is similar to syntometrine in the prevention of postpartum hemorrhage for women who have vaginal deliveries, with limited evidence showing a lower postpartum mean blood loss for women who received carbetocin compared to syntometrine. What is statistically and clinically significant is the much lower adverse effects experienced by women who received carbetocin compared to syntometrine [6]. In Bangladesh, though Oxytocin is included in the Essential Drug List as a registered uterotonic drug; Oxytocin is the choice of uterotonic in Bangladesh for Active management of the third stage of labor. Misoprostol is included in the Essential Drug List as a uterotonic drug [7]. Syntometrine is associated with a statistically significant reduction in the risk of postpartum hemorrhage when compared with oxytocin alone [8]. However, adverse effects of nausea, vomiting, and hypertension are higher in women receiving syntometrine because of the ergometrine component [9]. The primary purpose of active management of the third stage of labor is to reduce the risk of PPH. Prevention of postpartum hemorrhage is essential in the pursuit of improved health care for women. Over the past two decades, several other alternatives have been explored including the use of prostaglandins such as misoprostol and carboprost. The role of various prostaglandins including misoprostol for postpartum hemorrhage prophylaxis is limited. Among the agents that have been studied, oxytocin agonist (carbetocin) appears to be the most promising for this indication [10-13]. Carbetocin is a long-acting synthetic octapeptide analog of oxytocin with agonist properties. In pharmacokinetic studies, intravenous injections of carbetocin produced tetanic uterine contractions within 2 minutes, lasting 6 minutes, followed by rhythmic contractions for a further hour. Intramuscular injection produced tetanic contractions in <2 minutes, lasting about 11 minutes, and followed by rhythmic contractions for an additional 2 hours. The prolonged duration of activity after intramuscular compared with the intravenous carbetocin was significant. In comparison with oxytocin, carbetocin induces a prolonged uterine response when administered postpartum, in terms of both amplitude and frequency of contractions [10, 13].

OBJECTIVE

General Objective

- To analyze the adverse effects of carbetocin administration in the third stage of labor.

Specific Objectives

- To assess the age distribution of the study subjects.
- To know the use of additional uterotonics and blood transfusion in the patients.
- To assess the amount of blood loss after using carbetocin.

METHODS

This cross-section observational study was conducted at the Department of Obstetrics and Gynaecology, Shaheed Suhrawardy Medical College Hospital, Dhaka, Bangladesh. The study period was from May 2016 to October 2016. 100 women undergoing normal vaginal delivery were the study subject. A convenient sampling technique was used in this study. Necessary data was collected in the data collection sheet. Women received a bolus of 100 microgram carbetocin IV at delivery of the anterior shoulder. A standardized deliver mat (Quaiyum's mat) was used before placental removal for measuring blood loss, which was also measured by pre weighted sanitary pad. Blood loss was measured from each of the pregnant women within 24 hours of the postpartum period. Women were advised to preserve their soaked pads. Women received a bolus of 100 microgram carbetocin IV at delivery of the anterior shoulder. Blood loss, the uterine contraction was assessed by clinical examination of the uterus per abdominally, the need for additional uterotonics, the need for blood transfusion, and side effects of carbetocin within 24 hours of delivery. Statistical analysis was carried out by using the Statistical Package for Social Sciences version 19.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Before the commencement of this study, written and, or verbal approval was taken. All the information and records were kept confidential. Ethical clearance was obtained from the institutional ethics committee.

Inclusion Criteria

- Women of gestational age more than 36 weeks of pregnancy with labor pain.
- Patients who had given consent to participate in the study.

Exclusion Criteria

- Women with multiple pregnancies
- Placenta previa.
- Abruption placentae.
- Pregnancy with severe anemia
- Known cases of cardiac, renal, or liver disorder
- Hypersensitivity to carbetocin
- Unwilling to participate in the study.

RESULTS

Table 1: Distribution of the study patients by age, (N=100)

Age (years)	N	%
<20	16	16.0
20-25	54	54.0
>25	30	30.0
Mean±SD	23.6±4.04	
Range (min-max)	(18-30)	

In this study, the majority (54, 54.0%) of patients belonged to age 20-25 years, followed by (30, 30.0%) >25 years (Table 1).

Table 2: Distribution of the study patients by menstrual history and clinical indices, (N=100)

History / Indices	N	%
Menstrual history		
Regular	93	93.0
Irregular	07	07.0
Clinical indices		
Anemia	69	69.0
Jaundice	08	8.0
Edema	24	24.0

It was observed that the majority 93(93.0%) patients had regular menstrual history. Concerning the clinical indices, anemia was found 69(69.0%), jaundice 08(8.0%) and edema 24(24.0%) (Table 3).

Table 3: Additional uterotonics and blood transfusion using the third stage of labor, (N=100)

	N	%
Additional uterotonics		
Yes	15	15.0
No	85	85.0
Blood transfusion		
Yes	07	7.0
No	93	93.0

Additional uterotonices was used in 15(15.0%) and blood transfusion 07(7.0%) patients (Table 4).

Table 4: During the normal delivery amount of blood loss, (N=100)

	Blood loss	
	Mean	**±SD**
Before the use of the weight of Q-mat (in grams)	74.81	±1.23
After the use of the weight of Q-mat (in grams)	246.28	±99.98
Net blood loss (in grams)	141.61	±59.33
Amount of blood loss within 24 hours		
Before using the weight of the sanitary pad (in grams)		
2 hrs after delivery	45.76	±5.44
12 hrs after delivery	44.71	±4.49
24 hrs after delivery	43.45	±8.69
After the use of the weight of the sanitary pad (in grams)		
2 hrs after delivery	135.4	±20.19
12 hrs after delivery	101.3	±18.77
24 hrs after delivery	69.86	±10.24
After the use of the weight of the sanitary pad (in grams)		
2 hrs after delivery	81.93	±28.61
12 hrs after delivery	56.29	±18.77
24 hrs after delivery	24.00	±11.81

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Mean blood loss before the use of the weight of Q-mat was found 74.81±1.23 gram, mean blood loss after the use of the weight of Q-mat was 246.28±99.98 gram, and mean net blood loss was 141.61±59.93 gram.

Regarding the amount of blood loss within 24 hours before the use of the weight sanitary pad (in grams) mean blood loss 2 hours after the delivery was 45.76±5.44 grams, the mean blood loss 12hrs delivery was 44.71±4.49 grams, the mean blood loss 24 hours after delivery 43.45±8.69 gram.

After the use of a weight sanitary pan, the mean blood loss 2 hours after the delivery was 135.4±20.19 gram, the mean blood loss 12 hours after the delivery was 101.3±18.27 gram, the mean blood loss 24 hours after the delivery was found 69.86±10.24 gram.

After the use of a weight sanitary pad, the mean blood loss 2 hours after the delivery was 81.93±28.61 gram, the mean blood loss 12 hrs after delivery was 56.29±18.77 gram, and the mean blood loss 24 hours after delivery was 24.00±11.81 gram (Table 5).

Table 5: Distribution of the study patients by Hb% before delivery, (N=100)

Hb% before delivery (gm/dl)	N	%
<10.5	68	68.0
≥10.5	32	32.0
Mean±SD	10.3±0.47	
Range (min-max) (9.40-11.20)		

The table shows Hb% before delivery, it was observed that the majority 68(68.0%) patients had Hb% <10.5. Mean Hb% before delivery was 10.3±0.47 gm/dl with a range from 9.40 to 11.20 gm/dl (Table 4).

Table 6: Birth weight of the baby, (N=100)

Birth weight (kg)	N	%
1.5-2.4	39	39.0
≥2.5	61	61.0
Mean±SD	2.57±0.41	
Range (Min-max)	(2-3.10)	

It was observed that the majority of 61(61.0%) babies had birth weight ≥2.5 kg. The mean birth weight was found 2.57±0.41 kg with a range from 2.3 to 3.10 kg (Table 6).

DISCUSSION

In this study, the majority (54, 54.0%) of patients belonged to age 20-25 years, followed by (30, 30.0%) >25 years**.** A study by Su *et al*., [10] showed mean age was found 28.8±5.8 years with a range from 16.8 to 46.5 years. It was observed in this study that the majority 93(93.0%) patients had regular menstrual history. Concerning the clinical indices, anemia was found 69(69.0%), jaundice 08(8.0%) and edema 24(24.0%). Compared with the study by Tasmin *et al*., [14] showed among the study population 67.1% of patients had mild anemia before delivery. Nausea complaints only 4.3%, abdominal pain only 5.7%, vomiting only 4.3%, and headache only 4.3% which was not statistically significant. According to Chong *et al*., [13] active management of the third stage of labor is superior to expectant management in terms of blood loss, postpartum hemorrhage, and other serious complications, but is associated with unpleasant side effects and hypertension when ergometrine is included. Intramuscular oxytocin results in fewer side effects. Oral and rectal misoprostol has been extensively assessed and found to be less effective than conventional oxytocics with more side effects. Until alternative regimes of misoprostol are studied in large controlled trials, misoprostol is not recommended for routine use in the third stage of labor. Of the remaining uterotonic agents evaluated, intramuscular carbetocin appears the most promising. Mean blood loss before the use of the weight of Q-mat was found 74.81±1.23 gram, mean blood loss after the use of the weight of Q-mat was 246.28±99.98 gram, mean net blood loss was 141.61±59.93 gram in the present study. Askar *et al*., [15] found that, a single dose of intramuscular carbetocin 100 µg may be more effective as compared to a single intramuscular dose of syntometrine in reducing postpartum blood loss with a smaller drop in hemoglobin levels and fewer adverse effects. According to Leung *et al*., [16] the use of carbetocin was associated with a significantly lower incidence of nausea (relative risk [RR] 0.18, 95% confidence interval [CI] 0.04–0.78), vomiting (RR 0.1, 95% CI 0.01–0.74), hypertension 30 minutes (0 versus 8 cases, $P < 0.01$) and 60 minutes (0 versus 6 cases, $P < 0.05$) after delivery but a higher incidence of maternal tachycardia (RR 1.68, 95% CI 1.03–3.57). Intravenous carbetocin is effective in preventing primary postpartum hemorrhage after vaginal delivery. It is less likely to induce hypertension and has a low incidence of adverse effects. It should be considered a good alternative to conventional uterotonic agents used in managing the third stage of labor. Su LL, *et al*., stated in their study that, carbetocin is associated with less blood loss compared to syntometrine in the prevention of PPH for women who have vaginal deliveries and is associated with significantly fewer adverse effects and the risk of adverse effects such as nausea and vomiting were significantly lower in the carbetocin group [6]. In this present study, it was observed that the majority of 61(61.0%) babies had birth weight ≥2.5 kg. The mean birth weight was found 2.57±0.41 kg with a range from 2.3 to 3.10 kg. Compared with the study of Tasmin *et al*., [14] showed the mean body weight of babies was 2.96±0.4 Kg. Approximately similar results were found by Leung *et al*., [16] they showed that mean birth weight was found 3204±443 grams.

Limitations of The Study

The study was conducted in a single hospital with a small sample size. So, the results may not represent the whole community.

CONCLUSION

Carbetocin appears to be an effective new drug in the active management of third-stage labor. Carbetocin has associated with a lower risk of various adverse effects and preventing postpartum hemorrhage in women undergoing vagainal delivery.

Funding: No funding sources.

Conflict of interest: None declared.

Ethical approval: The study was approved by the Institutional Ethics Committee.

RECOMMENDATION

Carbetocin led to prompt and sustained uterine involution with a firm uterine tone. Moreover, further studies should be conducted involving a large sample size and multiple centers in this context.

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