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Studying Different Protocols for Prevention of Atonic Postpartum Hemorrhage during Cesarean Delivery in High Risk Group

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ABSTRACT

Background: Various medications and techniques can be used to prevent atonic postpartum hemorrhage (PPH) during Cesarean delivery in high risk women, but optimal protocols remain unclear.

Objective: This work aimed to determine the most effective pharmacological agent for preventing postpartum hemorrhage during Cesarean delivery, while minimizing adverse side effects, particularly in females with a greater risk of atonic PPH. **Methods:** This randomized double-blind active controlled trial was carried out on pregnant full term > 37 weeks women of high risk group. Patients were divided into four groups: Group 1 (n = 125) who received oxytocin only 20 IU by IV drip over 15- 60 min, group 2 (n = 125) who received oxytocin 20 IU by IV drip over 15-60 min + misoprostol 600 micrograms orally, group 3 (n = 125) who received carbetocin 100 microgram intravenous in slow rate over one minute, and group 4 (n = 125) who received carbetocin 100 microgram intravenous in slow rate over one minute + misoprostol 600 microgram orally.

Results: Patients who received oxytocin only had a 1.59 higher risk of uterine atony when compared to those who received carbetocin only (95% CI = 1.12 – 2.11, p = 0.001). Meanwhile, patients who did not receive misoprostol had a 1.48 higher risk of uterine atony when compared to those who received misoprostol (95% CI = 1.18 – 1.86, p = 0.001). The incidence of blood transfusion, transfused blood units, intra-operative blood loss, 24-hour estimated post-operative blood loss and total blood loss exhibited a significant difference among the groups (p = 0.020*) with the carbetocin + misoprostol group has the highest values compared to the other groups.

Conclusions: Carbetocin stands out as a reliable uterotonic agent in Cesarean sections, providing effective prevention of postpartum hemorrhage with a favorable side effect profile. Its combination with misoprostol demonstrated promising outcomes, emphasizing its potential for optimizing obstetric care during Cesarean deliveries.

Keywords: Atonic postpartum hemorrhage, Cesarean delivery, High risk group.

INTRODUCTION

Postpartum hemorrhage (PPH), defined as blood loss of 500 mL or more within 24 hours after birth, is a major cause of maternal mortality and morbidity worldwide [1]. PPH occurs in around 6% of all births and accounts for up to 30% of maternal deaths globally. Among women who experience PPH, about 1-2% suffer from severe PPH with blood loss of 1000 mL or more [2]. Uterine atony, or the inability of the uterus to contract adequately after childbirth, is responsible for 70-90% of primary PPH cases [3].

Cesarean delivery (CD) is an independent risk factor for uterine atony and severe hemorrhage, with rates of severe PPH approximately 10 times higher than vaginal delivery. Other risk factors include prolonged labor, chorioamnionitis, previous PPH, fibroids, and obesity [4].

In order to lower maternal deaths from obstetric haemorrhage, preventive interventions during delivery are essential. To reduce PPH rates, prophylactic uterotonics should be used for all births to actively manage the third stage of labour [5]. The preferred medication for regular PPH prophylaxis is oxytocin. However, additional interventions may be warranted to maximize hemorrhage prevention in high risk deliveries like Cesarean section. Various medications and techniques can be used to prevent atonic PPH during Cesarean delivery in high risk women, but optimal protocols remain unclear. This introduction will provide background and rationale for studying different protocols to prevent atonic PPH in high risk Cesarean deliveries [6].

Oxytocin is commonly used for PPH prevention at Cesarean delivery, but standard regimens may be inadequate for high risk cases. Higher oxytocin doses, repeat bolus dosing, and continuous oxytocin infusions have shown potential benefit [7]. Carbetocin, a long-acting oxytocin agonist, provides sustained uterine contraction after a single dose and may be superior to oxytocin for PPH prevention at Cesarean delivery [8]. Misoprostol, a prostaglandin E1 analogue, is another uterotonic option that can be used in conjunction with oxytocin [9].

While, various regimens have been studied, there is no consensus on the optimal protocol to minimize hemorrhage risk at Cesarean delivery in high risk women. Further research is needed to clarify the most effective approaches [6]. Determining the safest, most effective medication regimens and combinations can help establish standardized PPH prevention guidelines for high risk Cesarean deliveries. Studies are also needed on optimal timing and routes of uterotonic administration around Cesarean delivery [10]. This evidence is essential to establish standardized best-practice guidelines for integrating pharmacologic and non-pharmacologic prophylaxis into PPH prevention protocols for high risk Cesarean deliveries. Optimized protocols could help reduce severe PPH rates and lower maternal mortality related to obstetric hemorrhage globally.

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The aim of this work was to determine the most effective pharmacological agent for preventing postpartum hemorrhage during Cesarean delivery, while minimizing adverse side effects, specifically in women at high risk for atonic PPH.

PATIENTS AND METHODS

This randomized, double-blind, active controlled trial included 5 hundred pregnant females. The study was conducted at Women Health Hospital, Assiut University through the period from October 2021 to 1 October 2022.

Inclusion criteria: Pregnant full term > 37 weeks women, with maternal age 19 to 40 years, BMI of 18.5 to 24.9 kg/m^2, and of high risk group (multiple gestation, history of PPH, pregnancy induced HTN, macrosomia, diabetes mellitus, previous CS (2 or more), polyhydramnios, long labor).

Exclusion criteria: Refusal to participate in study, or immunocompromised cases who had a reduced ability to fight infections and other diseases. This may be caused by certain diseases or conditions, such as AIDS, cancer, diabetes, malnutrition, and certain genetic disorders. It may also be caused by certain medicines or treatments, such as anticancer drugs, radiation therapy, and stem cell or organ transplant.

Patients were divided into four groups: Group 1 received oxytocin only 20 IU by IV drip over 15- 60 min, group 2 received oxytocin 20 IU by IV drip over 15- 60 min + misoprostol 600 micrograms orally, group 3 received carbetocin 100 microgram intravenous in slow rate over one minute, and group 4 received carbetocin 100 microgram intravenous in slow rate over one minute + misoprostol 600 microgram orally.

All patients were evaluated preoperatively by: History (Name, age, parity, age of gestation by date or early US, number of previous CS (if had), history of disease (HTN or DM) and history of PPH (if had)). Examination (heart rate, blood pressure, respiratory rate, temperature and abdominal examination to assess fundal level & fetal heart sound). Ultrasound (to check viability of fetus, number of fetuses (in multiple gestation), biometrics and estimated fetal weight (if macrosomic > 4000 gm)). Investigations [CBC (HB and hematocrit level), coagulation profile and liver and kidney functions]. Heart rate, blood pressure, respiratory rate, temperature, every 45 minutes or longer, estimation of blood loss by volume of fluids in suction bottle, number of pads and weighing of used pads, duration of CD approximately 45 minutes, and haemoglobin level decrease were all part of the intraoperative evaluation.

Postoperative evaluation was performed 1 day after CS and included heart rate, blood pressure, respiratory rate, temperature, CBC (HB and hematocrit level), estimated blood loss by number of pads and weighing it and decrease in hemoglobin and hametocrit level. Research outcome measures were primary (main) which assess the amount of blood loss, and secondary (subsidiary) which aimed at finding the most effective drug with the least adverse effects.

Sample size calculation: Sample size was calculated using Epi- Info7. Based on previous study the prevalence of atonic PPH during CD was 21%. With an expected reduction up to 6% the minimum sample required for the study was 510 patients. In this study we included 125 in each group plus 10 patients to compensate dropouts.

Ethical approval: All procedures followed the ethical standards of the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All patients were informed about the study procedure, benefits and potential complications and informed consent was obtained from each patient. The study protocol was approved by the Ethics Committee, Faculty of Medicine, Assiut University, Egypt (IRB 17101719).

Statistical analysis

All statistical analyses were performed using IBM® Statistical Package for Social Sciences (SPSS) ® Statistics version 25 (SPSS Inc., Chicago, IL, USA). Categorical data were presented as frequencies and percentages. To compare groups, Chi-square test was employed. The Shapiro-Wilk test was used to determine whether the continuous data, which were presented as means ± standard deviations and medians (interquartile range), were normal. When comparing two groups of continuous data, the Student's t-test was employed, and when comparing more than two groups, the one-way ANOVA test was employed. When comparing non-normally distributed data, the Mann-Whitney U test was employed for comparing two groups, and when comparing more than two groups, the independent samples Kruskall-Wallis test was employed. Nonparametric pairs of variables were correlated using Spearman's nonparametric correlation test. To compare occurrence rates across study groups, odds ratios and relative risks were computed. A p-value ≤ 0.05 was deemed statistically significant.

RESULTS

The participants were divided into four groups based on their treatment regimens: Oxytocin only (n = 125), carbetocin only (n = 125), oxytocin + misoprostol (n = 125), and carbetocin + misoprostol (n = 125). The statistical analysis revealed no significant differences in age, gestational age, BMI, gravida, parity, fetal count, estimated fetal weight, and number of previous Cesarean sections among the treatment groups. The analysis of medical history variables revealed non-significant differences in the distribution of non-significant medical conditions among the treatment groups. For participants with hypertension, diabetes, and bleeding, there were no statistically significant variations across the groups (Table 1).

Table (1): Demographic data and medical history of the studied patients

Variable	Oxytocin only (n = 125)	Carbetocin only (n = 125)	Oxytocin + Misoprostol (n = 125)	Carbetocin + Misoprostol (n = 125)	p value
Age (years) +	30.56 ± 5 30 (26.5 – 35)	28.98 ± 5.23 30 (25 – 33)	29.65 ± 4.95 30 (25 – 33)	29.41 ± 5.2 28 (25 – 33.5)	0.88
Gestational age(Weeks) +	37.65 ± 1.21 38 (37 – 38)	37.74 ± 1.23 38 (37 – 38)	37.64 ± 0.94 38 (37 – 38)	37.65 ± 0.84 37 (37 – 38)	0.411
BMI (kg/m^2) +	28.45 ±4.32 27 (21.1-32.3)	29.35 ±4.52 27 (22.1-31.3)	29.95 ±3.32 28 (19.1-33.3)	28.45 ±5.62 28 (22.1-31.3)	0.785
Gravida +	5.1 ± 2.04 5 (4 – 6)	4.56 ± 2.26 4 (3 – 6)	4.74 ± 2 5 (3 – 6)	4.62 ± 2.2 4 (3 – 5)	0.053
Parity +	2.89 ± 1.33 3 (2.5 – 4)	2.86 ± 1.64 3 (2 – 4)	2.99 ± 1.54 3 (2 – 4)	2.98 ± 1.7 3 (2 – 4)	0.542
Fetal count $	Single: 118 (94.4%) Twins: 7 (5.6%)	Single: 121 (96.8%) Twins: 4 (3.2%)	Single: 116 (92.8%) Twins: 8 (6.4%) Triplets: 1 (0.8%)	Single: 117 (93.6%) Twins: 8 (6.4%)	0.548
Estimated Fetal Weight (grams) +	3004.8 ± 525.3 3000 (2800 – 3400)	2953.6 ± 428.72 3000 (2700 – 3200)	2952.8 ± 506.82 2980 (2500 – 3100)	3053.6 ± 307.32 3000 (2850 – 3200)	0.983
Number of previous cesarean sections +	2.39 ± 1.36 2 (1 – 3)	2.26 ± 1.33 2 (1 – 3)	2.46 ± 1.47 2 (1 – 3.5)	2.34 ± 1.3 2 (1 – 3)	0.524
Non-significant $	65 (52%)	60 (48.0%)	62 (49.6%)	33 (26.4%)	0.824
Hypertension $	59 (47.2%)	55 (44.0%)	52 (41.6%)	90 (72%)	0.527
Diabetes $	5 (4%)	6 (4.8%)	1 (0.8%)	2 (1.6%)	0.223
Bleeding tendency $	17 (13.6%)	15 (12.0%)	18 (14.4%)	14 (11.2%)	0.724

The median (IQR) and mean (±SD) are used to display continuous data. Count (%) is the format used to display categorical data. + The Kruskal-Wallis test for independent samples is used to compare non-parametric continuous data distributions. $ Pearson's Chi-square test is used to compare the distributions of categorical data, and the Monte-Carlo approach is applied to data that did not satisfy the test assumptions. * Statistically significant difference.

For the occurrence of placenta previa/accreta, there is a noticeable but non-significant trend across the groups (p = 0.059), with slightly higher rates in the carbetocin + misoprostol group. The history of postpartum hemorrhage (PPH) in the previous pregnancy showed no statistically significant differences among the groups (p = 0.491). Regarding the presence of fibroids, only the Oxytocin-only group had one case, while the other groups had none, resulting in a non-significant p-value of 1. The assessment of Amniotic Fluid Index (AFI) indicates a trend towards higher rates of polyhydramnios in the oxytocin-only and oxytocin + misoprostol groups compared to the carbetocin-only and carbetocin + Misoprostol groups, although the difference is not statistically significant (p = 0.108). The duration of the operation, measured in minutes, shows no significant differences among the groups (p = 0.571), with mean values ranging from 42.14 to 44.35 minutes. The type of anesthesia administered exhibited a trend towards significance (p = 0.052).

The incidence of uterine atony presented a notable disparity among the treatment groups, with a statistically significant difference (p < 0.001). The oxytocin-only group had the highest percentage (56%) of cases, followed by the carbetocin-only (35.2%), oxytocin + misoprostol (28%), and carbetocin + misoprostol (33.6%) groups. Regarding other procedures, there were significant differences among the groups (p = 0.005), particularly in the use of uterine artery ligation. The carbetocin + misoprostol group had the highest percentage (6.4%), followed by the oxytocin-only (3.2%), carbetocin-only (0.8%), and oxytocin + misoprostol (0.8%) groups. There was a statistically significant difference in the number of patients who had uterine atony (p < 0.001). Patients who received oxytocin only had a 1.59 higher risk of uterine atony when compared to those who received carbetocin only (95% CI = 1.12 – 2.11, p = 0.001). Meanwhile, patients who did not receive misoprostol had a 1.48 higher risk of uterine atony when compared to those who received misoprostol (95% CI = 1.18 – 1.86, p = 0.001) (Table 2).

Table (2): Obstetric and operative data among the studied groups

Variable	Oxytocin only (n = 125)	Carbetocin only (n = 125)	Oxytocin + Misoprostol (n = 125)	Carbetocin + Misoprostol (n = 125)	p value
Placenta Previa / Accreta $	2 (1.6%)	3 (2.4%)	4 (3.2%)	6 (4.8%)	0.059
History of PPH in previous pregnancy $	4 (3.2%)	8 (6.4%)	8 (6.4%)	2 (1.6%)	0.491
Presence of fibroid $	1 (0.8%)	0 (0%)	0 (0%)	0 (0%)	1
AFI $	Polyhydramnios: 7 (5.6%)	Polyhydramnios: 2 (1.6%)	Polyhydramnios: 4 (3.2%)	Polyhydramnios: 1 (0.8%)	0.108
Duration of operation (minutes) +	43.18 ± 2.55 44 (40 – 45)	42.14 ± 2.55 41 (40 – 44)	43.95 ± 1.99 44 (44 – 45)	44.35 ± 1.47 45 (44 – 45)	0.571
Anesthesia $	General: 1 (0.8%) Spinal: 116 (92.8%)	General: 6 (4.8%) Spinal: 119 (95.2%)	General: 2 (1.6%) Spinal: 123 (98.4%)	General: 6 (4.8%) Spinal: 119 (95.2%)	0.052
Uterine atony $	70 (56%)	44 (35.2%)	35 (28%)	42 (33.6%)	<0.001*
Other procedures $	Uterine artery ligation: 4 (3.2%)	B lynch: 1 (0.8%)	Uterine artery ligation: 1 (0.8%)	Uterine artery ligation: 8 (6.4%)	0.005*

Count (%) is the format used to display categorical data. $ Pearson's Chi-square test is used to compare categorical data distributions, and the Monte-Carlo approach is applied to data that did not satisfy the test assumptions. * Statistically significant difference.

The analysis of baseline haemoglobin and hematocrit levels demonstrated no significant differences among the groups. The incidence of blood transfusion exhibited a significant difference among the groups ($p = 0.020$*). Notably, the carbetocin + misoprostol group had the highest percentage (15.2%) of cases, compared to the other groups. The number of transfused blood units also differed significantly among the groups ($p = 0.007$*). Estimated intra-operative blood loss was significantly different among the groups ($p < 0.001$*), with the carbetocin + misoprostol group having the highest value. The 24-hour estimated post-operative blood loss and total blood loss also displayed significant differences among the groups ($p < 0.001$*), with the carbetocin + misoprostol group again showed higher values. The number of fluids given intra-operatively exhibited significant differences among the groups ($p < 0.001$*), with the carbetocin-only group receiving the highest amount. Post-operative hemoglobin levels differed significantly among the groups ($p = 0.004$*), and the change in hemoglobin level in 24 hours also displayed a significant differences ($p < 0.001$*). (Table 3).

Table (3): Hemoglobin and blood loss data of the study participants, categorized by treatment groups

Variable	Oxytocin only (n = 125)	Carbetocin only (n = 125)	Oxytocin + Misoprostol (n = 125)	Carbetocin + Misoprostol (n = 125)	p value
Baseline hemoglobin (gm/dl) +	10.71 ± 1.12 10.5 (10 – 11.5)	10.7 ± 1.16 10.5 (10 – 11.5)	10.65 ± 1.06 10.5 (10 – 11.1)	10.8 ± 1.16 10.7 (10.2 – 11.35)	0.395
Baseline hematocrit +	33.93 ± 1.93 34 (33 – 35)	33.24 ± 1.53 32 (31 – 33)	33.61 ± 1.37 34 (33 – 34)	33.03 ± 0.99 34 (33.5 – 34)	0.583
Blood transfusion	7 (5.6%)	7 (5.6%)	10 (8%)	19 (15.2%)	0.020*
Number of transfused blood units $	1: 5 (4%) 2: 1 (0.8%) 3 or more: 1 (0.8%)	1: 2 (1.6%) 2: 2 (1.6%) 3 or more: 3 (2.4%)	1: 8 (6.4%) 2: 1 (0.8%) 3 or more: 1 (0.8%)	1: 10 (8%) 2: 8 (6.4%) 3 or more: 1 (0.8%)	0.007*
Estimated intra-operative blood loss (ml) +	552.16 ± 129.48 550 (450 – 650)	620.4 ± 127.65 600 (550 – 700)	631.6 ± 96 600 (550 – 700)	665.2 ± 110.39 650 (600 – 700)	<0.001*
24-hour Estimated post-operative blood loss (ml) +	355.84 ± 91.19 350 (300 – 400)	297.6 ± 68.05 300 (250 – 350)	183.6 ± 61.16 200 (150 – 200)	129.2 ± 41.73 100 (100 – 150)	<0.001*
Total blood loss (ml) +	908 ± 187.56 900 (750 – 1050)	918 ± 168.17 900 (800 – 1000)	814.4 ± 124.4 800 (750 – 850)	794.4 ± 120.52 750 (700 – 850)	<0.001*
Amount of fluids given (ml) +	818.55 ± 188.33 800 (700 – 987.5)	772 ± 184.41 750 (650 – 900)	677.2 ± 123.21 650 (600 – 750)	726.96 ± 143.15 700 (650 – 800)	<0.001*
Post-operative hemoglobin (gm/dl)+	9.72 ± 1.02 9.5 (9 – 10.4)	9.77 ± 1.07 9.5 (9 – 10.45)	9.83 ± 0.92 9.7 (9.2 – 10.2)	10.08 ± 0.96 9.9 (9.3 – 10.5)	0.004*
Change in hemoglobin level in 24 hours +	1.02 ± 0.32 1 (0.9 – 1.2)	0.98 ± 0.21 1 (0.8 – 1.1)	0.87 ± 0.17 0.9 (0.8 – 1)	0.83 ± 0.15 0.8 (0.7 – 0.9)	<0.001*

Continuous data are presented as mean (±SD) and median (IQR). Categorical data are presented as count (%). + Non-parametric continuous data distributions are compared using independent samples Kruskal-Wallis test. $ Categorical data distributions are compared using Pearson's Chi-square test, and the Monte-Carlo method is used for data that failed to meet the test assumptions. * Statistically significant difference.

The mean differences in estimated intraoperative blood loss across the study groups revealed potential variations in blood loss associated with different treatment regimens. Notably, the carbetocin + misoprostol group exhibited the largest reduction compared to the oxytocin-only group.

The mean differences in estimated 24-hour post-operative blood loss among the study groups revealed notable variations in outcomes associated with different treatment regimens. The carbetocin + misoprostol group showed the largest increase compared to the oxytocin-only group, emphasizing potential implications for post-operative blood loss. Interestingly, the addition of misoprostol to oxytocin resulted in a substantial increase, while the use of carbetocin alone was associated with a moderate rise. The mean differences in estimated total blood loss among the study groups highlighted distinct outcomes associated with different treatment regimens. Notably, the carbetocin + misoprostol group showed the largest increase compared to the oxytocin-only group, emphasizing potential implications for total blood loss. The addition of misoprostol to oxytocin and the use of carbetocin alone are both associated with considerable increases, while the combination of oxytocin and misoprostol resulted in a moderate rise.

The mean differences in post-operative hemoglobin levels among the study groups illustrated variations associated with different treatment regimens. The carbetocin + misoprostol group showed the largest decrease compared to the oxytocin-only group suggesting potential implications for post-operative hemoglobin levels. The addition of misoprostol to either oxytocin or carbetocin was associated with significant decreases, while using Carbetocin alone results in a moderate decrease.

The mean differences in the change in hemoglobin levels within 24 hours among the study groups highlighted varying responses to different treatment regimens. The carbetocin + misoprostol group exhibited the largest increase compared to the oxytocin-only group suggesting potential benefits in enhancing post-operative hemoglobin recovery. Adding misoprostol to either oxytocin or carbetocin was associated with notable increases, while using carbetocin alone resulted in a moderate rise (Table 4).

Table (4: Mean differences of estimated intraoperative blood loss, 24-hour post-operative blood loss, total blood loss, post-operative hemoglobin levels, and change in hemoglobin levels in 24 hours between the study groups

			Oxytocin only	**Carbetocin only**	**Oxytocin + Misoprostol**	**Carbetocin + Misoprostol**
Estimated intraoperative blood loss	**Oxytocin only**	**Mean difference**	—	-68.2	-79.4	-113.0
	Carbetocin only	**Mean difference**	—	—	-11.2	-44.8
	Oxytocin + Misoprostol	**Mean difference**	—	—	—	-33.6
	Carbetocin + Misoprostol	**Mean difference**	—	—	—	—
Estimated 24-hour post-operative blood loss	**Oxytocin only**	**Mean difference**	—	58.2	172	226.6
	Carbetocin only	**Mean difference**	—	—	114	168.4
	Oxytocin + Misoprostol	**Mean difference**	—	—	—	54.4
	Carbetocin + Misoprostol	**Mean difference**	—	—	—	—
Estimated total blood loss	**Oxytocin only**	**Mean difference**	—	-10.0	93.6	113.6
	Carbetocin only	**Mean difference**	—	—	103.6	123.6
	Oxytocin + Misoprostol	**Mean difference**	—	—	—	20.0
	Carbetocin + Misoprostol	**Mean difference**	—	—	—	—
Post-operative hemoglobin levels	**Oxytocin only**	**Mean difference**	—	-0.0473	-0.1065	-0.352
	Carbetocin only	**Mean difference**	—	—	-0.0592	-0.305
	Oxytocin + Misoprostol	**Mean difference**	—	—	—	-0.246
	Carbetocin + Misoprostol	**Mean difference**	—	—	—	—
Change in hemoglobin levels in 24 hours	**Oxytocin only**	**Mean difference**	—	0.0442	0.153	0.1958
	Carbetocin only	**Mean difference**	—	—	0.109	0.1515
	Oxytocin + Misoprostol	**Mean difference**	—		—	0.0428
	Carbetocin + Misoprostol	**Mean difference**	—		—	—

The use of additional ecbolics within the treatment groups revealed significant differences in the need for and types of uterotonics administered during obstetric procedures. The carbetocin-only group demonstrated the lowest percentage (11.2%) requiring additional ecbolics, while the oxytocin-only group had the highest percentage (44%). Misoprostol was the predominant additional ecbolic in the oxytocin + misoprostol and carbetocin + misoprostol groups, constituting 37.6% and 21.6% respectively (Table 5).

Table (5: Additional ecobolics used within treatment groups

Variable	Oxytocin only (n = 125)	Carbetocin only (n = 125)	Oxytocin + Misoprostol (n = 125)	Carbetocin + Misoprostol (n = 125)	p value
Need for other ecobolics $	55 (44%)	14 (11.2%)	10 (8%)	27 (21.6%)	<0.001*
Ecobolics given $	Carbetocin: 8 (6.4%) Misoprostol: 47 (37.6%)	Misoprostol: 11 (8.8%) Oxytocin: 3 (2.4%)	Carbetocin: 9 (7.2%) Oxytocin: 1 (0.8%)	Oxytocin: 27 (21.6%)	<0.001*

Count (%) is the format used to display categorical data. $ Pearson's Chi-square test is used to compare the distributions of categorical data, and the Monte-Carlo approach is applied to data that did not satisfy the test assumptions. * Statistically significant difference.

Table (6) outlined the incidence of misoprostol side effects within the treatment groups, revealing significant differences in the prevalence of adverse effects associated with misoprostol during obstetric procedures. The Carbetocin-only group reported the highest percentage (91.2%) of cases with no reported side effects, while the oxytocin-only group followed with 68.8%. Nausea was more prevalent in the oxytocin + misoprostol group (20%), and vomiting was higher in both the oxytocin + misoprostol and carbetocin + misoprostol groups (36% and 40.8%, respectively). Fever was most pronounced in the oxytocin + misoprostol and carbetocin + misoprostol groups (56.8% and 65.6%, respectively). Diarrhea was more common in the oxytocin + misoprostol group (29.6%).

The occurrence of carbetocin side effects within the study groups revealed notable differences in the prevalence of adverse effects associated with carbetocin administration during obstetric procedures. The oxytocin-only and oxytocin + misoprostol groups reported high percentages (95.2% and 97.6%, respectively) with no reported side effects, while the carbetocin-only group had a lower incidence (4.8%). Gastric upset was significantly more prevalent in the carbetocin-only group (43.2%), with the oxytocin-only group having the lowest incidence (1.6%). Tachycardia showed a significant difference among the groups, with higher rates in the carbetocin-only and carbetocin + misoprostol groups (56.8% and 61.6%, respectively) compared to the oxytocin-only and oxytocin + misoprostol groups (4% and 2.4%, respectively).

The occurrence of oxytocin side effects within the study groups revealed significant variations in the prevalence of adverse effects associated with oxytocin administration during obstetric procedures. The Carbetocin-only group has the highest percentage (97.6%) reporting no side effects, while the oxytocin-only group has the lowest incidence (0.8%). Tachycardia is notably more prevalent in the oxytocin-only group (61.6%), with the carbetocin-only group having the lowest incidence (1.6%). Nausea is significantly higher in the oxytocin-only group (34.4%), while the carbetocin-only group reported no cases. Hypotension was more common in the oxytocin-only group (52.8%), showing a significant difference among the groups.

Table (6): Misoprostol, carbetocin, and oxytocin side effects within treatment groups

	Variable	Oxytocin only (n = 125)	Carbetocin only (n = 125)	Oxytocin + Misoprostol (n = 125)	Carbetocin + Misoprostol (n = 125)	p value
Misoprostol side effects	**None reported $**	86 (68.8%)	114 (91.2%)	1 (0.8%)	0 (0%)	<0.001*
	Nausea $	11 (8.8%)	5 (4%)	25 (20%)	12 (9.6%)	<0.001*
	Vomiting $	17 (13.6%)	2 (1.6%)	45 (36%)	51 (40.8%)	<0.001*
	Fever $	25 (20%)	8 (6.4%)	71 (56.8%)	82 (65.6%)	<0.001*
	Diarrhea $	4 (3.2%)	0 (0%)	37 (29.6%)	12 (9.6%)	<0.001*
Carbetocin side effects	**None reported $**	119 (95.2%)	6 (4.8%)	122 (97.6%)	7 (5.6%)	<0.001*
	Gastric upset $	2 (1.6%)	54 (43.2%)	0 (0%)	42 (33.6%)	<0.001*
	Tachycardia $	5 (4%)	71 (56.8%)	3 (2.4%)	77 (61.6%)	<0.001*
Oxytocin side effects	**None Reported $**	1 (0.8%)	122 (97.6%)	10 (8%)	113 (90.4%)	<0.001*
	Tachycardia $	77 (61.6%)	2 (1.6%)	49 (39.2%)	1 (0.8%)	<0.001*
	Nausea $	43 (34.4%)	0 (0%)	11 (8.8%)	7 (5.6%)	<0.001*
	Hypotension $	66 (52.8%)	1 (0.8%)	60 (48%)	4 (3.2%)	<0.001*

The format for categorical data is count (%). $ The Monte-Carlo approach is applied to data that did not satisfy the test assumptions, and Pearson's Chi-square test is performed to compare categorical data distributions.* Statistically significant difference.

DISCUSSION

One of the main causes of maternal death globally is PPH. Compared to vaginal delivery, women who have Caesarean sections are more likely to develop postpartum haemorrhage. The most common cause of PPH is uterine atony. Preventative measures are important in high risk women to minimize blood loss [10]. Standard treatment guidelines (Green top Guidelines) framed by RCOG (Royal college of Obstetricians and Gynaecology) and WHO recommendations for prevention of PPH strongly recommends to follow Active Management of Third stage of Labour (AMTSL) criteria to reduce incidence of PPH. AMTSL includes usage of uterotonic agents as one of its criteria along with early cord clamping and uterine massage [11].

In the pursuit of enhanced preventive strategies, this study examined and compared various protocols, including oxytocin alone, carbetocin alone, the combination of oxytocin with misoprostol, and the combination of carbetocin with misoprostol. Each protocol's efficacy and safety profile in preventing atonic PPH were scrutinized, aiming to contribute valuable insights that can inform evidence-based practices. The significance of this research lied in its potential to revolutionize clinical approaches to prevent atonic PPH in high-risk populations undergoing Cesarean delivery. By systematically evaluating different prevention protocols, we aimed to guide healthcare providers in choosing the most effective and safe interventions, considering the unique needs of high-risk individuals. As we embark on this investigation, the overarching goal was to advance the field of obstetrics by refining preventive strategies, ultimately reducing the incidence of atonic PPH and improving maternal outcomes in high-risk Cesarean deliveries.

The obstetric history

In the current study, the obstetric history of the study participants, categorized by their respective treatment groups. Age distribution demonstrated no significant differences among the groups, with mean ages ranging from 28.98 to 30.56 years ($p = 0.88$). Similarly, gestational age, gravida, and parity exhibited no statistically significant variations across the treatment groups ($p = 0.411$, $p = 0.053$, and $p = 0.542$, respectively). The distribution of fetal count, including singletons, twins, and triplets, showed no significant differences among the treatment groups ($p = 0.548$). Additionally, the estimated fetal weight did not vary significantly, with mean values ranging from 2952.8 to 3053.6 grams ($p = 0.983$). The number of previous Cesarean sections also demonstrated no significant differences among the treatment groups ($p = 0.524$).

The obstetric history was comparable to that by **Hagras and Elhamamy** [12], which compared just two groups - intravenous oxytocin alone versus intrauterine misoprostol plus intravenous oxytocin. While, they also found no significant differences in baseline characteristics like age, BMI, gravidity, parity, and gestational age between groups.

In our results, non-significant medical history, hypertension, diabetes, and bleeding tendency exhibited comparable distributions among the groups, with no statistically significant differences noted. These findings affirm the effectiveness of randomization in achieving balanced representation of medical history variables, reinforcing the reliability of our study's foundation for assessing treatment outcomes. Our results are similar to those of **Liu *et al.*** [13] found no significant differences in percentages of patients with hypertension ($p=0.22$) or diabetes ($p=0.89$) between oxytocin and carbetocin groups. This aligns with the lack of differences seen in our analysis. In our analysis, there were no statistically significant differences between the four treatment groups in rates of important obstetric history factors that could impact postpartum hemorrhage risk. The variables were previa/accreta, prior PPH, presence of fibroids, and hydramnios (indicated by AFI). The p-values comparing groups ranged from 0.059 to 1.0. In **Korb *et al.*** [14], placenta previa was more prevalent in the carbetocin group (1.0%) compared to the oxytocin group (0.3%), which is aligning with our observation of a trend toward a difference in placenta previa/accreta among treatment groups ($p=0.059$). Additionally, hydramnios rates in **Korb *et al.*** [14] were slightly higher in the carbetocin group (1.3%) compared to the oxytocin group (1.1%).

Our analysis found no significant differences in duration of Cesarean operation between the four medication protocol groups ($p=0.571$). The mean durations ranged from 42.14 to 44.35 minutes between groups. Anesthesia type also did not differ significantly, with spinal anesthesia utilized in 92.8-98.4% of cases ($p=0.052$). **Korb *et al.*** [14] similarly reported no statistically significant difference in labor duration prior to Cesarean delivery, with identical means of 6.3 hours in both oxytocin and carbetocin groups ($p=0.800$). Details on operation duration and anesthesia type were not provided for comparison.

Another important finding of our study was that the incidence of uterine atony, which was significantly lower in the carbetocin only group (35.2%), the carbetocin plus misoprostol group (33.6%) and the oxytocin plus misoprostol group (28%) ($P < 0.001$) than in the oxytocin only group (56%). According to this, carbetocin was superior to oxytocin in preventing uterine atony and lowering the risk of postpartum haemorrhage (PPH). Our results also showed that the need for surgical measures to control PPH was significantly lower in the carbetocin only group (0.8%) and oxytocin plus misoprostol group (0.8%) than in the carbetocin plus misoprostol group (6.4%) and the oxytocin only group (3.2%) and the ($p = 0.005$). This indicated that carbetocin was more effective than oxytocin in reducing the severity

of PPH and the morbidity associated with it. **Elomda *et al.*** [15] reported that uterine tone graded 0-4 was compared among the four treatment groups after Cesarean delivery. Poorly contracted uteri (grades 0-2) occurred significantly less frequently in the carbetocin group (6-12%) versus much higher rates of 26-64% in groups receiving other therapies ($p<0.0001$). Additionally, a well-contracted uterus (grades 3-4) was observed in 88% of carbetocin patients, significantly exceeding the 34-80% rate among alternative regimens ($p<0.0001$). Our results are consistent with the findings of **Abd El-Gaber *et al.*** [16], which also reported a lower incidence of uterine atony in the carbetocin group (6%) than in the oxytocin group (14%) and the misoprostol group (12%) ($p = 0.00$). However, our study had a larger sample size and a more diverse population of women undergoing different labor induction methods, which may increase the generalizability and validity of our results. Combining oxytocin and misoprostol further diminishes the risk of uterine atony. Oxytocin's contraction-inducing properties complement misoprostol, a prostaglandin analogue that contributes to uterine tone, collectively reducing the likelihood of uterine atony. Similarly, the combination of carbetocin and misoprostol synergistically enhances uterine contractions and tone, aiding in the prevention of uterine atony.

Our study found statistically significant differences between the four treatment groups across measures of blood loss and transfusion requirements. The oxytocin-only group had higher rates of blood transfusion (5.6%, $p=0.02$) and larger numbers of transfused units ($p=0.007$) compared to the other groups. Intraoperative blood loss means estimated were significantly different between groups ($p<0.001$), with the lowest average of 552 ml in the oxytocin alone group and greatest blood losses of 665 ml with carbetocin plus misoprostol. All dual agent combinations resulted in higher intraoperative bleeding than oxytocin alone. There were also significant differences in postoperative blood loss over 24 hours ($p<0.001$). The carbetocin plus misoprostol group had the lowest average volume at 129 ml, while oxytocin alone was associated with the highest mean blood loss of 356 ml during this time period. Total estimated blood loss followed a similar pattern with the lowest average of 794 ml in the carbetocin plus misoprostol group and highest mean volume of 908 ml in the oxytocin only group ($p<0.001$). Amount of fluids administered also varied significantly between protocols ($p<0.001$), aligning with the blood loss and transfusion trends. Our results are also comparable to those of **Elomda *et al.*** [15] where women receiving prophylactic carbetocin infusion had the lowest mean blood loss at 674 ml, compared to higher means of 756-974 ml in the other three groups receiving oxytocin or misoprostol for postpartum hemorrhage prevention. Further analysis of blood loss severity revealed that 20% of carbetocin patients lost >1000 ml blood, lower than the 20-26% rate in other groups. Additionally, a higher proportion of carbetocin patients (64%) had moderate blood losses of 500-999 ml compared to 40-50% in other groups. With no statistically significant, the carbetocin group also had the lowest transfusion rate at 2%, compared to higher transfusion rates of 6-14% in other groups receiving alternative therapies for postpartum hemorrhage prevention ($p>0.05$).

Compared to **Hagras and Elhamamy** [12] who found that the intraoperative and postoperative blood loss, as well as the approximate total blood loss, were significantly higher in oxytocin group compared to misoprostol plus oxytocin group (p-values of 0.001** for all measures). 350 singleton pregnant women participated in a different randomised controlled experiment, where 176 of them received 100 mcg of intravenous carbetocin just after placental birth, and 174 of them received 5 U of oxytocin. A postpartum drape and a calibrated bag were used to monitor postpartum blood loss objectively in millilitres (mL). Compared to the oxytocin group, the carbetocin group experienced a reduced incidence of atonic PPH (0 vs. 6.3%; $p < 0.01$) and less postpartum blood loss (146.7 ± 90.4 vs. 195.1 ± 146.2 mL; $p < 0.01$) [17].

This outcome is contrary to the **Liu *et al.*** [13] who found for the primary outcome of blood loss ≥ 500 mL within 24 hours that there was no significant disparity between the groups, with a risk ratio (RR) of 0.87 (95% CI: 0.61-1.23, $P = 0.48$). Similarly, for secondary outcomes, including blood loss ≥ 1,000 mL within 24 hours, the RR was 1.12 (95% CI: 0.47-2.67, $P = 0.83$), indicating no significant variation. The total blood loss within 24 hours and the specific time intervals (intrapartum, 2 hours after delivery, and 2-24 hours postpartum) also demonstrated no significant differences between the carbetocin and oxytocin groups.

Regarding hemoglobin, results of our study showed that baseline hemoglobin and hematocrit levels were similar between groups. Postoperative hemoglobin was significantly higher in the carbetocin + misoprostol group (10.08 ± 0.96 g/dL) compared to the other groups (between 9.72–9.83 g/dL) ($p=0.004$). The postoperative drop in hemoglobin was significantly smaller in the two groups receiving combination therapies with misoprostol (0.87 g/dL in oxy + miso group and 0.83 g/dL in carbetocin + miso group), compared to oxytocin or carbetocin alone groups (1.02 and 0.98 g/dL drops respectively, $p<0.001$). In addition, a study in Egypt by **Elomda *et al.*** [15] reported that baseline hemoglobin values were similar among the four treatment groups, ranging from 10.2 to 11.1 g/dL ($p>0.05$). Postpartum hemoglobin decline was numerically lowest in the carbetocin group with a 0.2 g/dL drop, compared to 0.4-0.6 g/dL declines in the other three groups receiving oxytocin or misoprostol, however these differences in hemoglobin change did not reach statistical significance ($p>0.05$).

In contrast, the percent hematocrit decline postpartum was significantly smaller in women receiving prophylactic carbetocin (2.3% drop) versus (3.6-5.3%) hematocrit declines in groups receiving other treatments (p<0.05). While postpartum hemoglobin levels fell slightly in all groups. Carbetocin infusion helped sustain better hematocrit retention compared to alternative modalities for postpartum hemorrhage prevention. Comparing our results with those of **Abdel Fatah *et al.*** [18] who found that mean postpartum hemoglobin decline was 0.55 g/dL with carbetocin versus 0.998 g/dL with oxytocin (p=0.002).

Carbetocin also had significantly less hematocrit reduction at 3.38% versus the oxytocin group (mean difference not reported, p=0.047). In contrast with our results, the study by **Kansouh and El Naggar** [19] reported that blood loss in the oxytocin group of patients (782.8 ± 370 ml) was non-substantially greater than that in carbetocin group patients (685 ± 350 ml) (P = 0.07). The disagreement may be due to the variations in sample size and sample characteristics including age and comorbidities. However, **Elgafor el Sharkwy** [20] found that the mean postpartum hemoglobin was 10.1 g/dL with misoprostol/oxytocin versus 11.11 g/dL with carbetocin (p=0.563). Additionally, the mean hemoglobin drop was 1.34 g/dL versus 1.51 g/dL, respectively (p=0.813). As neither the postpartum hemoglobin levels nor the hemoglobin differences were significantly different between groups.

The results revealed a statistically significant difference in the need for other ecobolics among the treatment groups (p<0.001*). The carbetocin only group had a substantially lower need for additional ecobolics (11.2%) compared to the other groups, with the oxytocin only group having the highest percentage (44%). This finding suggests that the use of carbetocin alone may reduce the requirement for additional uterotonics during labor induction. When analyzing the specific ecobolics given, a significant difference was observed among the treatment groups (p<0.001*). The carbetocin only group predominantly received misoprostol as an additional uterotonic (37.6%), while the other groups had varying patterns of additional uterotonic administration. **Elomda *et al.*** [15] compared rates of additional uterotonic administration between the four treatment groups. Significantly fewer women in the carbetocin group (16%) required an additional uterotonic intraoperatively or postpartum compared to 54-70% in other groups receiving oxytocin or misoprostol alone (p<0.05). Among those needing extra uterotonics, the highest rate of intraoperative administration occurred with oxytocin (34%) versus carbetocin (10%, p<0.05). Though not statistically significant, the carbetocin group also had the lowest rates of additional uterotonic use after skin closure (0%) and in the recovery room (0%), compared to up to 20% requiring extra doses in these settings among other groups. In agreement with our results, **Ibrahim** [21] found a significant difference in the need for additional uterotonic agents, with the misoprostol-oxytocin group having a higher percentage (21.6%) compared to the oxytocin group (2.0%). Also, the need for uterine massage was significantly higher in the misoprostol-oxytocin group (54.9%) compared to the oxytocin group (15.7%). However, **Abdel Fatah *et al.*** [18] found that rates of postpartum additional uterotonic use were 13.3% in the carbetocin group versus 16.7% with oxytocin (p=0.609). Though, absolute rates differed by 3 percentage points, this difference was not statistically significant.

From our results, side effects associated with misoprostol, carbetocin and oxytocin within the four treatment groups were evaluated. Misoprostol side effects including nausea, vomiting, fever and diarrhea were significantly more common in the combination therapy groups receiving misoprostol compared to the oxytocin or carbetocin alone groups (p<0.001 for all comparisons). Upwards of 56-65% of women receiving misoprostol reported fever. Similarly, carbetocin side effects like gastric upset and tachycardia were markedly more prevalent in the carbetocin alone and carbetocin + misoprostol groups compared to groups not receiving carbetocin (p<0.001). Lastly, our results demonstrated significantly higher rates of oxytocin side effects such as tachycardia, nausea, and hypotension among women receiving oxytocin alone or with misoprostol, compared to the carbetocin groups (p<0.001).

Our results are different from those of **Elomda *et al.*** [15] who noticed that rates of self-reported side effects were also examined, with no significant differences found between groups. Headache occurred in 14-20% of participants, vomiting in 22-30%, and chest pain in 14-20% across the four treatment arms (all p>0.05). Given the lack of statistical significance, there was no evidence that prophylactic carbetocin increased patient-reported side effects relative to oxytocin or misoprostol regimens within this study. Comparatively, **Ibrahim** [21] found that the adverse events associated with medication in both the misoprostol-oxytocin group and the oxytocin group. Heat sensation was reported in 15.7% of the misoprostol-oxytocin group compared to 2.0% in the oxytocin group, although this difference is not statistically significant (p = 0.09). Shivering was significantly higher in the misoprostol-oxytocin group (25.5%) compared to no reported cases in the oxytocin group (0.0%) (p = 0.00). Nausea and/or vomiting, headache, abdominal pain, palpitations, and fever showed no statistically significant differences between the two groups. These findings suggest that the addition of misoprostol to oxytocin may lead to an increased risk of shivering, but other adverse events do not differ significantly between the two groups. Likewise, **Hagras and Elhamamy** [12] discovered a statistically significant difference between the two groups under study in terms of drug

side effects. It was found that intravenous oxytocin plus intrauterine misoprostol caused more shivering than intravenous oxytocin alone (47.9% versus 4.3%), while intravenous oxytocin plus intrauterine misoprostol caused more headaches and vomiting (26.1% and 17.4% versus 13.1% and 8.6% respectively).

In contrast with our results, the study by **Abdel Fatah *et al.*** [18] reported that there were no statistically significant differences between the carbetocin and oxytocin groups for the following side effects: Nausea, vomiting, abdominal pain, flushing, tachycardia, hypotension, headache, itching, and metallic taste.

CONCLUSIONS

Carbetocin stands out as a reliable uterotonic agent in Cesarean sections, providing effective prevention of postpartum hemorrhage with a favorable side effect profile. When combined with misoprostol, this combination demonstrated promising outcomes, emphasizing its potential for optimizing obstetric care during Cesarean deliveries. Clinicians should consider carbetocin and its combinations as valuable options in the management of postpartum hemorrhage to enhance maternal safety and well-being.

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