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Carbetocin Versus Misoprostol in Prevention of Postpartum Hemorrhage in High Risk Patients

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ABSTRACT

Background: Postpartum hemorrhage (PPH) is a significant problem and a major cause of maternal mortality and morbidity, resulting in up to 28% of maternal deaths. It is a potentially life-threatening complication of both vaginal and cesarean delivery, the prevalence of PPH is approximately 6% of all deliveries.

Objective: The aim of this study is to compare the effectiveness and safety of carbetocin and misoprostol for the prevention of atonic postpartum hemorrhage in high risk patients.

Patients and Methods: this study is a prospective clinical study which was conducted at the Department of Obstetrics and Gynecology, Aswan University Hospital, in the period from September 2017 till September 2018. One hundred cases were involved in the study and divided into 2 equal groups.

The study was approved by the medical ethics committee of Aswan University Hospital and a written informed consent is obtained from all patients.

Results: Significant difference was found between the two studied groups as regard mean volume of blood loss. Carbetocin group showed the lowest volume of blood loss. As regard uterine tone after treatment, carbetocin group showed the highest tone compared to misoprostol groups. Significant difference was found between the two groups as regard need for additional uterotonics. The results demonstrated an increased use of additional oxytocics in the misoprostol group (32% of cases) VS (12% of cases) in carbetocin group.

Conclusion: According to the results of this study, it's concluded that carbetocin is more effective in controlling the amount of blood loss during delivery and eventually help in the prevention of postpartum hemorrhage in high risk patients.

Keywords: Carbetocin, Misoprostol, Postpartum Hemorrhage.

INTRODUCTION

Postpartum hemorrhage (PPH) is defined as blood loss in excess of 500 ml at vaginal delivery or 1000 ml at cesarean section. Loss of these amounts within 24 hours is termed early or primary PPH, whereas such losses are termed late or secondary PPH if they occur 24 hours after delivery [(1)].

Hemorrhage still continues to be reported as one of the leading causes of maternal mortality and morbidity. Intraoperative estimation of the blood loss seems to be complex and misleading as it is impaired by the amount of amniotic fluid and blood from the placenta [(2)].

The hemorrhage can result from uterine atony, retained placental tissue including that from abnormal placentation, maternal genital tract trauma and coagulopathies [(3)]. Uterine atony is the major cause of hemorrhage accounting for up to 80% of PPH cases [(4)].

Risk factors for PPH include suspected or proven placental abruption, known placenta previa, multiple pregnancy, pre-eclampsia and gestational hypertension, previous PPH, obesity (BMI >35), anemia (<9 g/dl), delivery by elective caesarean section, induction of labor, retained placental tissues, prolonged labor (> 12 hours) and big baby (> 4 kg) [(5)].

Several uterotonics agents are used to prevent PPH because of uterine atony, including oxytocin [(6)], ergot alkaloid [(7)] and prostaglandin [(8)].

Misoprostol is a prostaglandin (E1) analogue with strong uterotonic properties and has been suggested as an alternative to injectable uterotonic agents for preventing PPH [(9)]. It is cheap, heat stable, and can be administered through multiple routes [(10)]. Misoprostol has been widely recommended for the prevention of post-partum hemorrhage when other methods are not available. Rectal route is the most common regimen reported for the treatment of post-partum hemorrhage [(11)].

Carbetocin, a long-acting oxytocin analogue that bind to oxytocin receptors with higher affinity, its contractile effect of uterus is apparent within two minutes [(12)]. A 100-µg dose of carbetocin has been recommended for preventing PPH in high risk patients. An advantage of carbetocin over others uterotonics is that, owing to its long half-life, it is administrated as a single intravenous dose [(13)].

Oxytocin has a short half-life, whereas carbetocin is an oxytocin derivative exerting its effect via the same molecular mechanisms as oxytocin, has a longer half-life, and has been reported to decrease the use of additional oxytocin [(12)].

Currently 100 µg of carbetocin is used for the prevention of PPH. The hemodynamic effects of an oxytocin bolus consist of systemic vasodilatation, with hypotension, tachycardia, and an increase in cardiac output and pulmonary artery pressure, resulting in brief hypotension and tachycardia in a dose-dependent manner [(14)].

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AIM OF THE STUDY

The aim of this study is to compare the effectiveness and safety of carbetocin and misoprostol for the prevention of atonic postpartum hemorrhage in high risk patients.

PATIENTS AND METHODS

Study design:

1. **Type of the study**: prospective clinical study.
2. **Study Settings:** this study was conducted at the Department of Obstetrics and Gynecology, Aswan University Hospital, in the period from September 2017 till September 2018.
3. **One hundred cases were involved in the study and** divided into 2 equal groups.

Ethical approval and written informed consent:

The study was approved by the medical ethics committee of Aswan University Hospital and a written informed consent is obtained from all patients.

Inclusion criteria:

Parturient (with high risk for developing postpartum hemorrhage) were included in the present study.

1. Women undergoing delivery by vaginal or cesarean section after 28 weeks of gestation.
2. Any medical disorder with pregnancy that carries a risk factors for PPH as (PET, anemia , thrombocytopenia).
3. Uterine overdistention during pregnancy (twins; polyhydramnios; macrosomia).
4. Chorioamnionitis.
5. Prolonged labor.
6. Woman had previous history of atonic PPH.

Exclusion criteria:

1- Deliveries having no risk factors for postpartum hemorrhage.

Methodology:

For all patients included in the study the following was done:

1. On the day of delivery all parturient had obstetric ultrasonography for assurance of diagnosis and evaluation of fetal condition; and blood sample for complete blood counting was taken.
2. 100 Parturient were allocated into TWO equal groups each group involved 50 cases.
3. **Group (A):** received 100 mcg of carbetocin (Pabal 100 mcg Ferring Pharmaceuticals) as a single dose by direct intravenous injection over one minute immediately after delivery of the head.
4. **Group (B):** received 600 mcg (Misotac Sigma) (3 tablets) of misoprostol sublingual at the start of CS or rectal immediately after delivery of the head in the vaginal delivery.
5. The need for additional uterotonics agents (oxytocin, methylergometrine) was recorded. Duration of the operation and blood transfusion, maternal pulse rate, blood pressure and fetal body weight were also recorded.
6. Uterine tone was assessed immediately after delivery of the placenta and then every 5 minutes until the end of delivery**.**
7. Uterine tone was rated according to the extent of indentation by finger pressure using a 5-point scale with 0 indicate soft boggy uterus and 4 indicate rock hard tetanic uterus.
8. Additional uterotonic was administrated in the form of slow injection of oxytocin 20 IU. The frequency of additional uterotonic used since administration of study dose till 24 hours after delivery was also reported.
9. Estimation of blood loss began after suction of amniotic fluid and discarding it.
10. After delivery of the placenta, the volume of blood loss was assessed by weight by subtracting the dry weight of absorbing materials (pads, sponges, etc.) from the weight of blood-containing materials and using the conversion 1 gm weight = 1 ml to quantify the blood volume contained in the materials **.**

1- ***Post-operative care****:*

- Vital signs (pulse and BP) of the patients were measured every two hours during hospitalization.
- Complete blood count examination was done 24 hours after delivery.

Primary Outcomes:

1. Uterine tone and size: (Time Frame: during delivery and first 24 hours after delivery). The occurrence of uterine atony requiring the use of additional uterotonics is considered the primary outcome of this study. The uterine tone and size were assessed by using a hand resting on the fundus and palpating the anterior wall of the uterus every 30 minutes in 1st two hours after the delivery then every two hours. The presence of a boggy uterus with either heavy vaginal bleeding or increasing uterine size can suspect diagnosis of uterine atony.

Secondary Outcomes:

1. Blood loss: Blood loss was estimated by amount of blood in suction apparatus during delivery and by giving each woman of each group standard 2 dressings (standard weight of dressing is 25 gm) after delivery and recording weight of blood soaked dressings and volume of lost blood during 1st 24 hours.

The amount of blood loss was calculated according to number of soaked pads or dressing

used after delivery for the 1st 24 hours where each soaked dressing = 50 cc.

Intraoperative blood loss in cases delivered by CS:

Operative blood loss was calculated from the amount of blood in the suction bottle after delivery of placenta and the number of towel used and to which degree they were socked.

Blood from the uterine incision, soaked towels and blood in suction bottle before placental delivery was not added to the blood measurements.

- Soaked towel = 150 cc.
- Semi-soaked towel = 75 cc.

2. Hemoglobin concentration: Concentration of hemoglobin at 24 hours after delivery, or the change in concentration compared to baseline level.
3. Need for blood transfusion: Blood transfusion given during or within 24 hours after delivery.

Statistical analysis

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

The following tests were done:

- Independent-samples t-test of significance was used when comparing between two means.
- Chi-square (x^2) test of significance was used in order to compare proportions between two qualitative parameters.
- The confidence interval was set to 95% and the margin of error accepted was set to 5%. The p-value was considered significant as the following:

- Probability (P-value)
- P-value <0.05 was considered significant.
- P-value <0.001 was considered as highly significant.
- P-value >0.05 was considered insignificant.

RESULTS

Table (1): Obstetric history within the two groups

		Mean / N	SD / %
Age by years		29.23	5.82
Parity	PG	25	25.0%
	P1	17	17.0%
	P2	17	17.0%
	P3	18	18.0%
	P4	11	11.0%
	P5	9	9.0%
	P6	2	2.0%
	P7	1	1.0%
Abortion			
Abortion	0	75	75.0%
	1	17	17.0%
	2	6	6.0%
	3	2	2.0%

The mean age of patients was 29.23 years. PG represents (25 %) of cases while the majority of cases were P1- P3 (52 %) and had no previous abortions (79%).

Table (2): Gestational age and Risk factors for PPH within the two groups.

		Mean / N	SD / %
Gestational age by weeks		37.51	1.67
Risk factors for PPH	Anaemic	12	12.0%
	PET	20	20.0%
	Placenta previa	17	17.0%
	Gestational HTN	9	9.0%
	Twins	6	6.0%
	Chronic HTN	5	5.0%
	History of PPH	9	9.0%
	Macrosomia	4	4.0%
	Thrombocytopenia	7	7.0%
	Prolonged labour	1	1.0%
	Polyhydramnios	3	3.0%
	Antepartum heg	4	4.0%
	Chorioamnionitis	1	1.0%
	Triplet	1	1.0%
	Accidental heg	1	1.0%

PET and HTN were considered the main risk factors for PPH among 34% of cases. The median gestational age was (37- 38) weeks.

Comparison analysis

Table (3): Obstetric data between the two studied groups

		Group		Fisher's Exact test	
		Group A CARBETOCIN)	Group B (MISOPROSTOL)		
		Mean ± SD N (%) Median (IQR)	Mean ± SD N (%) Median (IQR)	P-Value	Sig.
Age by years		29.12 ± 6.16	29.34 ± 5.51	0.851(T)	NS
Parity	PG	13 (26%)	12 (24%)	0.923	NS
	P1	8 (16%)	9 (18%)		
	P2	9 (18%)	8 (16%)		
	P3	8 (16%)	10 (20%)		
	P4	6 (12%)	5 (10%)		
	P5	5 (10%)	4 (8%)		
	P6	0 (0%)	2 (4%)		
	P7	1 (2%)	0 (0%)		
Abortion	0	39 (78%)	40 (80%)	0.918	NS
	1	9 (18%)	7 (14%)		
	2	2 (4%)	2 (4%)		
	3	0 (0%)	1 (2%)		

(T) Student t-test of significance.

There was no significant difference between the two studied groups as regard patients' age, parity or history of previous abortions. The mean age among carbetocin cases and misoprotol cases was 29.12 ±6.16 and 29.34 ±5.51 years respectively.

Table (4) Comparison between Group (A) and Group (B) according to price

	Group	
	Group A (Carbetocin)	Group B (Misoprostol)
Brand names	Pabal	Misotac
	Duratocin	Misoprost
	Depotocin	Cytotec
Price	(Pabal) 110 LE / Amp	(Misotac) 6 LE / 3 Tabs, 20 LE/ Strep 10 tabs

There is great deference in the price between (Pabal) 110 LE / Amp and (Misotac) 6 LE / 3 Tabs**.**

Table (5): Gestational age *and risk factors for PPH between the studied groups.*

		Group		Fisher's Exact test	
		Group A (CARBETOCIN)	Group B (MISOPROSTOL)		
		Mean ± SD N (%)	Mean ± SD N (%)	P-Value	Sig.
Gestational age by weeks		37.36 ± 1.69	37.66 ± 1.65	0.371(T)	NS
Risk factors for PPH	Anaemic	7 (14%)	5 (10%)	0.999	NS
	PET	10 (20%)	8 (16%)		
	Placenta previa	9 (18%)	8 (16%)		
	Gestational HTN	3 (6%)	6 (12%)		
	Twins	4 (8%)	2 (4%)		
	Chronic HTN	2 (4%)	3 (6%)		
	History of PPH	4 (8%)	5 (10%)		
	Macrosomia	2 (4%)	2 (4%)		
	Thrombocytopenia	1 (2%)	3 (6%)		
	Prolonged labor	3 (6%)	2 (4%)		
	Polyhydramnios	1 (2%)	3 (6%)		
	Antepartum he	2 (4%)	2 (4%)		
	Chorioamnionitis	1 (2%)	0 (0%)		
	Triplet	1 (2%)	0 (0%)		
	Accidental he	0 (0%)	1 (2%)		

(T) Student t-test of significance. There was no significant difference between the two studied groups as regard patients' GA or risk factors for PPH. By using Student t-test.

Table (6): Mode of delivery and Hb between the two groups.

		Group		Test of significance	
		Group A (CARBETOCIN)	Group B (MISOPROSTOL)		
		Mean ± SD N (%)	Mean ± SD N (%)	P-Value	Sig.
Mode of delivery	NVD	20 (40%)	21 (42%)	0.839(C)	NS
	CS	30 (60%)	29 (58%)		
Hb before delivery		10.98 ± 0.98	10.82 ± 0.76	0.381(T)	NS
Hb 24 h after delivery		9.95 ± 1.02	9.26 ± 0.87	0.121(T)	NS

(C) Chi-Square test of significance.
(T) Student t-test of significance.

There was no significant difference between the two groups as regard mean haemoglobin level before and 24 h after treatment. However, the misoprostol group showing the higher drop in Hb (9.26 ± 0.87) compared to carbetocin group (9.95 ± 1.02) using Student t- test.

Table (7): Need for uterotonics, amount of blood loss and blood transfusion between the two studied groups.

	Group		Fisher's Exact test	
	Group A (CARBETOCIN)	Group B (MISOPROSTOL)		
	Mean ± SD N (%)	Mean ± SD N (%)	P-Value	Sig.
Need for uterotonics(No.of PPH Cases)	6 (12%)	16 (32%)	0.016(C)	S
Amount of blood loss by CC	702 ± 226.32	834 ± 227.33	0.004(T)	S
Need for blood transfusion	3 (6%)	6 (12%)	0.487	NS
Uterine tone(cases not entered in PPH)	44 (88%)	34 (68%)	0.016(C)	S
Adverse effect	2 (4%)	5 (10%)	0.436	NS

(C) Chi-Square test of significance.
(T) Student t-test of significance.

There was significant difference between the two groups as regard the need for additional uterotonics. By using Chi-Square test only 12% of carbetocin group needs for additional uterotonics while 32% of misoprostol group needs for additional uterotonics. But no significant difference was found between the two groups as regard need for blood transfusion and adverse effects.

There was significant difference between the two studied groups as regard mean volume of blood loss and mean uterine tone after treatment. Carbetocin group showed the lower volume of blood loss (702 ±226.32) compared to misoprostol (834 ±227.33). By using Student t-test, the significant difference was shown to be between carbetocin and misoprostol groups. As regard uterine tone after treatment, carbetocin group showed the higher tone compared to misoprostol group. By using Chi-Square test, the significant difference was shown to be between carbetocin and misoprostol groups.

DISCUSSION

In the present study the aim was to compare between the effect of carbetocin and misoprostol on decreasing blood loss and prevent PPH in high risk pregnant patients.

The study included 100 pregnant women divided into two equal groups and the following was done: Group A → received slow intravenous injection of a single dose of carbetocin 100 μg as soon as the umbilical cord is clamped immediately after delivery the head of baby. Group B → received 600 μg of misoprostol (3 tablets) sublingually immediately after delivery of the head.

Concerning need for additional uterotonics:

In our study, there was significant difference between the two groups as regard need for additional uterotonics.

The results demonstrated an increased use of additional oxytocics in the misoprostol group (32% of cases) VS (12% of cases) in carbetocin group.

The main result in a study done by **Larciprete *et al.*** [15] was that carbetocin was associated with reduction use of additional oxytocics.

In another study compared between carbetocin and misoprostol included cesarean and vaginal delivery done by **Ibrahim *et al.*** [16]**,** carbetocin significantly reduced the need for additional uterotonics.

Only one study by **Elbohoty *et al.*** [17] recorded no significant difference between carbetocin and

misoprostol in the reduction of the risk of severe PPH.

In our study, as regard **change of Hb of the women involved in this study:**

- In carbetocin group: the mean was (9.95) SD is± (1.02)
- In misoprostol group: the mean was (9.26) the SD is ± (0.87)

The results showed no significant difference between the two studied groups as regard mean change in hemoglobin level 24 h after treatment, however the misoprostol group showed the higher drop in Hb (9.26 ± 0.87) compared to carbetocin group (9.95 ± 1.02) by using Student t- test.

In the study done by **Mohamed *et al.*** [18] comparing carbetocin and misoprostol showed that the hemoglobin level was significantly lower in women who received misoprostol than in those who received carbetocin among women who underwent cesarean section. However, among women who had normal vaginal delivery, the hemoglobin was not significantly different between women who received carbetocin or misoprostol.

In another a study done by **Attilakos *et al.*** [12], comparing carbetocin and oxytocin: there was no significant difference in the mean hemoglobin fall after delivery.

Another study done by **Fazel *et al.*** [19] comparing rectal misoprostol to IV oxytocin, the decrease in Hb level in the two groups wasn't statistically significant. (P = 0.55).

As regard volume of blood loss:

Our work, showed that blood loss in the third stage of labor and in the postpartum period was significantly lower in women who received carbetocin (702 ± 226.32) than in those who received misoprostol (834 ±227.3) among women who underwent normal vaginal delivery and those who underwent cesarean section which coincided with the results done by **Mohamed *et al.*** [18] comparing carbetocin and misoprostol.

In a study done by **Mousa *et al.*** [20] comparing carbetocin, oxytocin and misoprostol the mean blood loss was observed to be greater in the misoprostol group compared to the carbetocin group and the difference was statistically significant.

In another study done by **Sallam *et al.*** [21] at Aswan University Hospital comparing misoprostol with placebo in reduced blood loss and prevention of PPH. It was found that high significant reduction in blood loss with misoprostol group than placebo group.

Concerning uterine tone after treatment

In our work, regarding uterine tone after treatment carbetocin group showed the highest tone compared to misoprostol group with a significant difference according to Chi-Square test.

This can be explained as carbetocin causes uterine contractions in less than 2 minutes after IV administration of optimal dosage of 100 μg. A single dose of carbetocin has been hypothysed to act as 16 hours after IV infusion regarding the increase in uterine tone and reduction of risk of post-partum Hge [15].

In a study done by **Larciprete *et al.*** [15] comparing carbetocin and oxytocin: there was significant difference in the uterine tone and in the fundal height. The uterine contractility was better in carbetocin group at 2.12 and 24 hours after delivery and the difference was statistically significant at 24 hours (P < 0.05)

Nevertheless, the lower use of additional oxytocics is an important outcome with possible financial savings if the additional oxytocics require prolonged administration or the labor ward or in the recovery area. However, this may be offset by the higher cost of carbetocin in comparison to misoprostol [12].

One limitation of the present study was comparing carbetocin and misoprostol without including a combination of misoprostol plus oxytocin as a comparator.

We note through this study when the risk factor for PPH was placenta previa (in carbetocin group 9 cases and in misoprostol 8 cases) 4 cases from carbetocin group enter in PPH and need for additional uterotonics, while all 8 cases of misoprostol group enters in PPH and need for additional uterotonics except one case. This means that misoprostol is not suitable to be used alone in cases of placenta previa.

As for our study, the cost of the carbetocin ampoule in Egypt is 110 LE which may be not applicable in most of the hospitals and among the Egyptian populations as Egypt is considered one of the developing countries, while the cost of misoprostol about 40 LE for 20 tablets (3 tablets 6 LE.). So, it is considered cheap and available in most of Egyptian hospitals.

CONCLUSION

According to the results of this study, there is good overall agreement that carbetocin is more effective and giving a better chance in prevention of atonic postpartum hemorrhage in high risk patient.

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