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Original Research Article

Carbetocin versus Oxytocin and Misoprostol in prevention of atonic post-partum hemorrhage in high risk patients planed for cesarean delivery

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ABSTRACT

Background: Post-partum hemorrhage prevention (PPH) is considered a major issue due to its effect on maternal morbidity and mortality. The objective of this study was to compare efficacy of Carbetocin in prevention of atonic post-partum hemorrhage in high risk patients undergoing elective caesarean section in comparison to Oxytocin and Misoprostol.

Methods: 150 pregnant women prepared for elective caesarean section were classified into 3 groups; Group I (50 patients received Carbetocin 100 mg I.V infusion), Group II (50 patients received 20 IU of Oxytocin infusion on 1000 ml of normal saline solution) and Group III (50 cases received Misoprostol 400 µg per rectum immediately before induction of anaesthesia). Assessment of PPH and its degree was determined according to amount of blood loss during and for first 24 hours of caesarean delivery, also further need for haemostatic measures were also assessed.

Results: There was a statistically significant difference in PPH among the three groups 6, 14 and 12% for group I, II and III respectively (P <0.001), major PPH was 0, 4 and 6% for the same groups respectively (P <0.001). The need for additional uterotonic agents was significantly lesser in Group I compared to Group II and III (2% versus 8 and 12% respectively P = 0.02) also the need for additional surgical measures was significantly lesser among the three groups (P= 0.00). The drop in Hb level and haematocrit value was significantly lesser in group I compared to group II& III (P <0.05). The need for blood transfusion was significantly lesser in Group I compared to group II and III (0% versus 12% p <0.0001)

Conclusions: Carbetocin was superior to Oxytocin and Misoprostol in prevention of atonic PPH in high risk patients underwent elective caesarean delivery. Carbetocin should be administered for all cases undergoing elective CS and carry a risk factor for postpartum hemorrhage.

Keywords: Carbetocin, Cesarean section, Misoprostol, Oxytocin, Postpartum hemorrhage

INTRODUCTION

Primary postpartum hemorrhage (PPH) is a major cause of maternal mortality, with a worldwide prevalence of ~6%.[1] PPH arises mainly from the failure of the uterus to contract after delivery, leading to blood loss of 500 ml in vaginal delivery, >1000 ml in cesarean section (CS), or a substantial drop in hematocrit compared with the antepartum level; those conditions may occur in the first 24 hours after delivery (primary PPH) or between 24 hours and 6 weeks after delivery (secondary PPH).[2,3] Risk factors for atonic PPH include history of prior PPH, large

baby, parity, prolonged or augmented labor, placental abnormalities, anemia, and CS, although it may also occur in women with no identifiable risk factors.[4,5] Post-partum hemorrhage Prevention (PPH) is considered a major issue due to its effect on maternal morbidity and mortality.[6] The majority of maternal deaths occur during first 4 hours of delivery, which indicates that they are consequence complications of the third stage of labor.[7]

Caesarean section is considered as a risk factor for atonic PPH and the worldwide incidence of caesarean section rate became horrible figures.[6] Oxytocin is a widely used and effective first choice uterotonic agent in the universal prevention of PPH.[8,9] It binds to Oxytocin receptors of the myometrium and stimulates uterine muscle contraction where it increases the intracellular calcium concentration.[10] However, there are some limitations of its use, beside Oxytocin has a short half-life of few minutes, and a continuous intravenous (IV) infusion is mandatory to have sustained uterine contraction.[11,12] Moreover, many side effects are associated with large doses or boluses of Oxytocin as hypotension, nausea, vomiting, severe water intoxication with or without seizures, dysrhythmias, ST-T changes and pulmonary edema.[13]

Misoprostol, an E1 prostaglandin analogue, induces uterine contractions and, because of this property, has several important uses in women's reproductive health programs. The efficacy of Misoprostol for PPH prevention has been well documented.[14]

Carbetocin (100 mg), a synthetic analogue of Oxytocin, can be given in elective CS as an IV bolus over 1 minute, instead of a continuous Oxytocin infusion, for the prevention of PPH and to decrease the need for therapeutic uterotonic agents.

With a plasma half-life of 40 minutes, Carbetocin has a longer duration of action than Oxytocin. It is indicated for the prevention of uterine atony and PPH following elective CS under epidural or spinal anaesthesia. Intravenous injection of Carbetocin produces rhythmic uterine contractions lasting approximately 60 minutes while IM injection significantly prolongs its activity ~120 minutes.[9]

The aim of this study was to find out the efficacy of Carbetocin in prevention of atonic post-partum hemorrhage in high risk patients undergo elective cesarean section in comparison to Oxytocin and Misoprostol.

METHODS

150 pregnant women prepared for elective caesarean section selected from those patients attended for delivery at Obstetrics and Gynecology Department of Qena and Al Azhar University Hospitals between October 2016 and August 2017 and had one or more risk factors of postpartum hemorrhage were included in this study. Risk factors include history of prior PPH, large baby, parity, prolonged or augmented labor, placental abnormalities, and anemia. A written consent was obtained from all patients participating in this study according to the Medical Ethics Committee.

Exclusion criteria

Patients with blood diseases as thrombocytopenia and coagulation defect, Renal and liver diseases, hypersensitivity to Carbetocin and any contraindication for Misoprostol as bronchial asthma were excluded from the study. Spinal anesthesia technique was standardized for all groups

Patients were classified into 3 groups

Group I

This group included 50 cases (Carbetocin group) (PAPAL) 100mg was administered iv slowly during cesarean section after delivery of baby.

Group II

This group included 50 cases (Oxytocin group) received 20 IU of Oxytocin iv infusion on 1000 ml of normal saline solution during cesarean section after delivery of baby,

Group III

This group included 50 cases (Misoprostol group) received Misoprostol 400ug per rectum immediately before induction of anesthesia in operating theater.

For all participants detailed history, physical examination (general, abdominal, and obstetric examination), routine laboratory tests (CBC, liver and renal function, urine analysis and coagulation profile) were obtained.

After placental delivery the uterine fundus was palpated for contractility and the amount and degree of blood loss from placental site were assessed by weighing of soaked towel and napkins, changes in hemoglobin and hematocrit values before and 48 hours after cesarean delivery and need for further hemostatic measures were assessed.

Post-partum hemorrhage was considered:

- Minor PPH: if estimated blood loss is up to 1000 ml.
- Major PPH: if any estimated blood loss is over 1000 ml.

Clinical observation of patients was continued for the first 24 hours (every 10 minutes in first hour and then every hour for remaining 23 hours) for reporting and management of any degree of postpartum hemorrhage.

Statistical methods

Results were expressed as Mean±SD or number and (%). Comparison between categorical data was performed using ANOVA test. The data was considered significant if p-values <0.05. Statistical analysis was performed with the aid of the SPSS (version 19) computer program.

RESULTS

Table 1 shows socio demographic characteristics of the study groups, there was no statistically significant difference as regard to maternal age, BMI, parity and gestational age (P >0.05).

Table 1: Socio demographic characteristics of the studied groups.

	Group I (n=50)	Group II (n=50)	Group III (n=50)	*P*
Age (years)	27.82±4.6	28.5±4.5	28.2±3.6	0.728
BMI (kg/m^2)	26.95± 3.8	27.72±4.6	26.87±3.9	0.498
Parity	2.3±1.81	2.2±1.74	2.3±1.78	0.744
Gestational age (weeks)	38.2±0.90	38.6±0.82	38.7±0.73	0.631

Values are given as mean ±SD

Table 2 shows the incidence of PPH and its degree in the studied groups. There were statistically significant differences among the three groups as regard to incidence of PPH and its major degree but a mildly statistically significant difference in its minor degree (P <0.001 and <0.05 respectively).

Table 3 shows the need for additional haemostatic measures to control bleeding. There was a mildly statistically significant difference among studied groups as regard to need for additional uterotonic agents as Ergometrine, a moderate significance as regard to the need for haemostatic surgical measures and a highly significant difference as regard to the need for blood transfusion with (P <0.05, <0.001 and <0.001 respectively).

Table 2: Incidence and degree of atonic PPH for the studied groups.

	Group I (n=50)	Group II (n=50)	Group III (n=50)	*P*
Incidence of PPH	3 (6%)	7 (14%)	6 (12%)	0.00**
Degree of PPG				
Minor	3 (6%)	5 (10%)	3 (6%)	0.074
Major	0 (0.0%)	2 (4%)	3 (6%)	0.000***

Values are given as (No. %); **moderate significance; *** high significance

Table 3: Need for additional medical or surgical lines to control bleeding for the studied groups.

Additional lines	Type	Group I (n=50)	Group II (n=50)	Group III (n=50)	P value
Uterotonic drugs	Ergometrine	1 (2%)	4 (8%)	6 (12%)	0.024 *
Surgical measures	Uterine artery ligation	0 (0%)	1 (2%)	3 (6%)	0.00**
	Compression sutures	0 (0%)	3 (6%)	4 (8%)	
	Hysterectomy	0 (0%)	1 (2%)	0 (0%)	
Blood transfusion	One unit	1(2%)	4 (8%)	3 (6%)	0.000***
	More than 1 unit	0(0.0)	2(4%)	3 (6%)	

Values are given as (No. %); *mild significance; **moderate significance; *** high significance

Table 4: Pre and post CS hemoglobin level and hematocrit value for the studied groups.

	Group I (n=50)	Group II (n=50)	Group III (n=50)	P- value
Hemoglobin (g/dl)				
Pre-operative	10.72±0.75	10.82±0.72	10.86±0.57	0.509
Post-operative	10.13±0.76	9.64±0.84	9.57±0.95	0.047*
Haematocrit value				
Pre-operative	32.94±2.63	33.06±3.56	33.06±3.56	0.848
Post-operative	28.26±2.94	27.20±2.71	27.31±2.77	0.043*

*mild significance

Table 4 shows the pre-and post-operative hemoglobin and haematocrit value levels in the studied group. There was a statistically significant difference among the three groups as regard to reduction of both parameters (p <0.04).

DISCUSSION

Primary PPH is one of five causes of maternal mortality in both developed and developing countries found. The most important risk factors for severe PPH were related to an abnormal third stage of labor whether prolonged >30 minutes or retained placenta.[15] The most common cause of PPH is uterine atony. This belief of being the most common cause is based upon the fact that, in most cases of moderate hemorrhage there was no evidence of retention of placental tissue or tears, and the bleeding has persisted until contraction of the uterus was induced.[16]

The aim of this study was to compare the efficacy of Carbetocin, Oxytocin and Misoprostol in preventing or minimizing the degree of postpartum hemorrhage in high risk patients undergoing elective cesarean section. There was no statistically significant difference between the three groups as regard to demographic data (maternal age, BMI, parity or gestational age). The incidence of postpartum hemorrhage was found in 6% (3 cases), 14 % (7 cases) and 12% (6 cases) in Carbetocin, Oxytocin and Misoprostol groups respectively and the difference was moderately statistically significant, these findings were in agreement to what was reported by Dansereau et al, 1999.[17]

Also, Larciprete et al found in their study that a single injection of Carbetocin appears to be more effective than a continuous infusion of oxytocin to prevent the PPH, with a similar hemodynamic profile and minor antidiuretic effect.[18]

As regard to severity of postpartum hemorrhage the incidence of major PPH was 0 (0%), 2 (4%) and 3 (6%) in Carbetocin, Oxytocin and Misoprostol respectively and the difference was highly statistically significant (P <0.0001). These results were in accordance with Chen et al, who found in their study comparing the effect of Carbetocin prophylaxis in vaginal and CS that a significant decrease in blood loss was noted with the prophylactic use of Carbetocin in cesarean deliveries.[9]

The use of prophylactic Carbetocin significantly decreased the incidence of PPH more in cesarean than in vaginal deliveries. They also stated that CS-related PPH often results in catastrophic problems, and often needs a complicated method for preservation of the uterus.

Therefore, the finding of a significant reduction of incidence of PPH for CS patients who were treated with Carbetocin prophylaxis might further suggest the risk of peripartum hysterectomy could also be decreased. Several studies discussed the efficacy of Carbetocin in prevention of postpartum hemorrhage during vaginal and cesarean deliveries. A single dose of 100 µg of Carbetocin given with intravenous drip has been proved to be as effective as a 16-hour infusion of Oxytocin in prevention of intraoperative and postoperative blood loss after caesarean section.[19] Another study found that a single dose of Carbetocin had the same efficacy compared to two-hour Oxytocin infusion in prevention of intraoperative blood loss after removal of placental.[20]

In the current study we found that the needed for additional uterotonic agents and or for further surgical hemostatic measures were lesser in Carbetocin group compared to the other two groups and the difference was statistically significant. Present finding is in accordance with Borruto et al and Larciprete et al who confirmed same findings.[20,18]

In the present study hemoglobin level and hematocrit value assessment preoperative and 48 hours postoperatively after elective cesarean delivery had a mildly significant difference among the three studied groups (p <0.05) so Carbetocin prevent or minimize incidence of post cesarean delivery hemorrhagic anemia.

In this study only one patients (2%) in Carbetocin group received one unit of blood post cesarean delivery while in Oxytocin group 4 patients (8%) received one unit and 2 patients (4%) received 2 units of blood and in Misoprostol group 3 patients (6%) received one unit of blood and 3 patients (6%) received two units of blood and the difference was statistically significant (p <0.001). these findings were comparable to Borruto et al, Chen et al.[20,9]

CONCLUSION

Carbetocin is superior to Oxytocin and Misoprostol in preventing and minimizing incidence of atonic postpartum hemorrhage in patients performing elective caesarean delivery with high risk factors.

Carbetocin is solely efficient in controlling postpartum hemorrhage and is associated with less need for further uterotonic agents or surgical haemostatic measures in comparison to Oxytocin and Misoprostol groups. It produces prolonged uterine tetanic spasm during and post cesarean delivery in comparison to Oxytocin and Misoprostol.

Recommendations

Carbetocin should be administered prophylactically in elective cesarean deliveries for all patients carry a risk factor for postpartum hemorrhage.

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