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Original Article

Carbetocin versus Rectal Misoprostol to Decrease Blood Loss in Vaginal Delivery in High Risk Patients for Postpartum Hemorrhage

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ABSTRACT

Background: Postpartum hemorrhage is a critical complication after delivery. Methods to decrease or prevent postpartum hemorrhage continue to develop. The medical prophylaxis is frequently used with extension of the utilized drugs.

Aim of the work: The current study aims to evaluate the effects of intravenous carbetocin versus rectal misoprostol to decrease blood loss in vaginal delivery in high risk patients for postpartum hemorrhage.

Patients and Methods: The study included 94 Patients. They were selected from those attending for normal vaginal delivery and categorized as high risk for postpartum hemorrhage. All were evaluated on clinical basis, laboratory investigations and abdominal ultrasound. Then patients were randomly assigned into two equal groups; group A [Carbetocin group] received 1 ampoule of Carbetocin [100 µg/ml] intravenously as a bolus injection slowly over one minute after neonatal delivery, and group B [Misoprostol group] received three rectal misoprostol tablets [600 µg] after neonatal delivery. Each group was assessed for hemodynamic changes [blood pressure, pulse and respiratory rate], gastrointestinal [GIT] side effects as nausea, vomiting and metallic taste, vasomotor effects as flushing, headache, itching.

Results: The amount of blood loss was significantly lower in the carbetocin group than in the misoprostol group [365.53±41.12 ml vs. 404.68±67.27 ml]. Need for uterotonics reported among 17.0% of misoprostol group compared to none [0.0%] in carbetocin group [P=0.003]. On the other side, need for blood transfusion and uterine massage was also increased in misoprostol than carbetocin groups, but the difference was not statistically significant. The complications [drug side effects] revealed that, there was significant increase of fever, nausea & vomiting, diarrhea and abdominal pain in misoprostol than carbetocin group [21.3%, 10.6%, 19.14% and 21.3% vs. 0.0%, 0.0%, 2.12% and 0.0% successively].

Conclusion: Carbetocin is superior to misoprostol for postpartum hemorrhage, regarding efficacy and safety.

Keywords: Postpartum; Hemorrhage; Carbetocin; Misoprostol, Vaginal Delivery.

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INTRODUCTION

Postpartum hemorrhage [PPH] diagnosis is settled when there is a blood loss of more than 500 ml in the first 24 hours after normal vaginal delivery or more than one litre after cesarean delivery. PPH is a critical etiology of maternal complications and even death after delivery. Active PPH management by uterotonic drugs will reduce its rate [1].

Obstetric hemorrhage represents 25% of maternal mortality in the developing world and PPH is the commonest type. PPH is responsible for 10.6% of all United Kingdom direct maternal deaths, and it is the third common etiology of maternal deaths [2]. As a result, the use of uterotonics during cesarean delivery or in active management of the third stage of normal labor has become essential to reduce the risk of PPH and decrease maternal morbidity and mortality [3].

The World Health Organization endorses active management for the third stage of labor, and the use of uterotonic such as oxytocin should be used as a prophylaxis against PPH in all females at delivery [4].

The first line medication for PPH is oxytocin administration; however, many studies reported that the sole administration of oxytocin is not sufficient and other non-drug methods are recommended. Other methods used to control PPH [not responded to oxytocin administration] include uterine massage, internal iliac artery ligation, uterine artery suturing, embolization, uterine package, and if not controlled, hysterectomy is the last resort [5].

There are further medications, other than oxytocin, to reduce or prevent PPH. The timing of administration is crucial. A previous trial showed that the use of oxytocin or methylergometrine immediately after delivery of the anterior shoulder of the fetus can markedly decrease the rate of PPH when compared to the use of uterotonics after delivery of the placenta [6].

Carbetocin is used to control PPH. It is an oxytocin-analogue, binds to the same oxytocin receptors, on the uterus smooth musculature, leading to rhythmic uterine contractions, increased frequency of the existing contractions, and augments the uterine tone [7]. Misoprostol is a prostaglandin E1 [PGE1] analogue, producing its action through G proteins which normally activate adenylate cyclase. The indirect inhibition of adenylate cyclase by misoprostol may be reliant on guanosine-5'-triphosphate [GTP]. Misoprostol also augments the amplitude and frequency of uterine contractions during gestation [8].

AIM OF THE WORK

Whatever the mechanism of action, the vital role for obstetrician is the prevention of PPH with minimal side effects. Thus, many drugs were tried continuously. The study aims at evaluating the effects of intravenous carbetocin versus rectal misoprostol to decrease blood loss in vaginal delivery in high risk patients for postpartum hemorrhage.

PATIENTS AND METHODS

The study was designed as a randomized comparative trial. It had been conducted at Obstetrics and Gynecology Department, Al-Azhar University [New Damietta] from December 2019 to December 2020. The study included 94 patients selected from those whom admitted for spontaneous or induced vaginal delivery and categorized as high risk for postpartum hemorrhage.

The inclusion criteria were high risk for postpartum hemorrhage [e.g., grand multiparity > 5 deliveries], uterine over distension due to any reason, prolonged second stage of labor, patients with history of postpartum hemorrhage in previous deliveries, and medical disorders [e.g. Diabetes, anemia and coagulation disorders].

On the opposite side, the exclusion criteria were history of hypersensitivity to carbetocin or misoprostol, traumatic PPH and medical disorders [e.g. cardiovascular diseases especially coronary artery diseases, valvular heart diseases, cardiomyopathy and heart failure, hepatic, renal diseases, serious vascular disorders and epileptic patients].

All Patients were subjected to clinical evaluation by detailed history, physical examination [general and local for progress of labor], and laboratory investigations [Complete Count of blood cells, and determination of blood groups]. Additionally, all patients were evaluated by obstetric ultrasound for fetal viability, gestational age, estimated fetal weight [EFW] and placental site. Then patients were randomly subdivided [closed envelope method] into 2 groups [A and B]; each group include 47 patients: Group A [Carbetocin group] received 1 ampoule of Carbetocin [100 µg/ml] [Pabal; Draxis, Multipharma, Egypt, under license from Draxis Pharma, Canada] intravenously as a bolus injection slowly over 1 minute after neonatal delivery. Group B [Misoprostol group] received three rectal misoprostol tablets [600 µg, Misotac; Sigma Pharma, Cairo, Egypt] after neonatal delivery.

Blood samples were used to measure hemoglobin levels on admission to the delivery room and at 24 hours post-delivery. After parturition of the neonatal anterior

shoulder, uterotonic agent [misoprostol or carbetocin] was administered. Then, we clamped the umbilical cord and it was separated after birth. A minimal tension was applied on the cord with abdominal counter pressure to the uterus at the same time. If the uterus was in atony or there was uncontrollable bleeding within 5 minutes of drug administration, an additional uterotonic drug was administered [intramuscular methergin] with or without uterine massage. The genital tract was thoroughly reviewed for detection and management of any tears [cervical or vaginal]. Any episiotomy [if carried out] was sutured. The measurement of blood loss was started directly after uterotonic drug administration.

Calculation of blood loss

The total volume of collected fluids in the under-buttocks towels was documented. The fluid volume collected in the towels was added to the volume measured by weighing soaked drapes. All blood-soaked drapes and clots were weighed to calculate cumulative volume. The equation used to calculate blood loss was wet items gram weight – the same dry item gram weight = milliliters of blood [9].

Complete blood count was done to compare between the efficacies of each drug in decreasing blood loss. Each group was assessed for hemodynamic changes, GIT side effects, vasomotor effects, headache and itching.

Sample Size

The sample size was calculated using the following formula [10]:

$$N = \left[\frac{z\alpha}{2} \sqrt{2pq} + z\beta \sqrt{p_1q_1 + p_2q_2} \right]^2$$

Where, N= sample size, $z\alpha / 2 = 1.96$ [the critical value that divides the central 95% of the z distribution from the 5% in the tail, $z\beta = 1.96$ [the critical value that separate the lower 5% of the z distribution from the upper 80%], $p = [p_1+p_2]/2$ [p_1 = proportional of bleeding 500 ml of blood in patients treated with misoprostol = 47%, p_2 = proportional of bleeding 500 ml of blood in patients treated with Carbetocin = 20 % [11], $q = [1-p]$. So, the sample size is equal to 94 subject total 47 subjects per group.

Ethical considerations

This study was approved by Institution Research Board [IRB] of Damietta faculty of medicine Al-Azhar University. Informed verbal consent was obtained from each participant sharing in the study. Confidentiality and personal privacy will be respected in all levels of the study.

Statistical analysis

Data were analysed using Statistical Program for Social Science [SPSS] version 24. Quantitative data were expressed as mean \pm standard deviation [SD]. Qualitative data were expressed as frequency and percentage. The test used for comparison was Chi square test, student "t" test and paired samples' "t" test for appropriate data. P-value < 0.05 was considered significant.

RESULTS

The age of the cases ranged from 15 years to 48 years with the mean age 30.02 ± 7.68 years. The mean gravidity number was 3.86 ± 2.5 times and the mean parity number was 2.13 ± 1.78 times. The mean body mass index for the participating cases was 30.59 ± 4.6 kg/m². The mean hemoglobin measured before delivery for the cases was 10.41 ± 1.4 g/dl. Two patients [2.13%] were smokers, 6.38% had gestational hypertension, 3.19% had diabetes mellitus, 2.13% had hypertension, 2.13% had chronic sinusitis, 1.06% had depression, 1.06% had chronic cholecystitis, 1.06% had hepatitis C-virus, and 1.06% had hypothyroidism. The obstetrics ultrasound revealed single viable fetus among 80.85%, 15.96% had dichorionic diamniotic viable twins, 2.13% had triplets viable and 1.06% had monochorionic monoamniotic viable twin. Results revealed that, 33.0% of patients had anemia, 9.6% had thrombocytopenia, 3.2% had polyhydramnios, the grand-multipara were 14.9%, and history of previous PPH was reported among 16.0% and history of antepartum hemorrhage was reported among 18.1%. The mean pulse measured for the participating cases was 72.8 ± 7.9 beat/minute. The mean systolic blood pressure measured for the cases was 104.8 ± 10.9 mmHg. The mean diastolic blood pressure measured for the cases was 68.4 ± 7.2 mmHg. The mean temperature measured for the cases was 37.3 ± 0.5 C°. The mean respiratory rate was 17.4 ± 1.0 breaths/minute. The mean hemoglobin measured after delivery for the cases was 10 ± 1.2 g/dl. The mean amount of blood loss of cases was 385.1 ± 58.8 cc. The need for uterotonics [methergin] was reported among 8.5%, need for blood transfusion indicated in 17.0% and need for uterine massage among 17.0%. Allergy reported among 2.1%, fever in 10.6%, nausea and vomiting among 5.3%, diarrhea in 10.6%, abdominal pain in 10.6%, facial flushing in 19.1%, and headache in 22.3%.

There were no statistically significant difference between means of hemoglobin level before and after delivery in cases that had misoprostol and the cases that had carbetocin. On the other hand, the amount of blood loss showed a statistically significant difference between the cases that had misoprostol and the cases that had

carbetocin as the mean was less in carbetocin group than in misoprostol group. Need for uterotonics reported among 17.0% of misoprostol group compared to none [0.0%] in carbetocin group, with significant difference. On the other side, need for blood transfusion and uterine massage was

also increased in misoprostol than carbetocin groups, but the difference was statistically non-significant. The complications [drug side effects] revealed that, there was significant increase fever, nausea and vomiting, diarrhea and abdominal pain misoprostol than carbetocin [Table 1].

Table [1]: Comparison between misoprostol and carbetocin groups regarding outcome

Variable	Group		P value	
	Misoprostol	Carbetocin		
Hemoglobin	Before delivery	10.11±1.40	10.51±1.41	0.17
	24 After delivery	9.78±1.23	10.18±1.22	0.11
Amount of blood loss [ml]		404.68±67.27	365.53±41.12	<0.001*
Need for uterotonics [methergin]		8 [17.0%]	0[0.0%]	0.003*
Need for blood transfusion		11 [23.4%]	5 [10.6%]	0.08
Need for uterine massage		10[21.3%]	6[12.8%]	0.41
Complications	Allergy	2[4.3%]	0 [0.0%]	0.153
	Fever	10[21.3%]	0 [0.0%]	0.001*
	Nausea and vomiting	5 [10.6%]	0 [0.0%]	0.022*
	Diarrhea	9[19.14%]	1 [2.12%]	0.007*
	Abdominal pain	10[21.3%]	0 [0.0%]	0.001*
	Facial flushing	9 [19.14%]	9 [19.14%]	1.0
	Headache	10[21.3%]	11 [23.4%]	0.80

DISCUSSION

PPH is the most common cause of maternal comorbidity and mortality. It is responsible for about 20% of maternal deaths worldwide [12]. The PPH could be due to uterine atony, retained placental parts, genital trauma and coagulopathies [13]. Uterine atony is the major etiology of PPH and is responsible for up to 70% of cases. As a result, several uterotonics are tried to prevent PPH, including oxytocin, ergot alkaloid and prostaglandin [14].

The current study focused on comparing between the effect of misoprostol and carbetocin on reducing loss of blood and prevention of PPH in high risk patients. The results in this study showed that neither administration of misoprostol nor Carbetocin had significant effect on the hemoglobin level. In line with the above results, a recent study by Ismail *et al.* [14] showed no significant difference between the carbetocin and misoprostol groups as regard mean change in hemoglobin level in the first day after treatment. Another study compared between carbetocin and misoprostol. The results showed that the hemoglobin was not significantly different between women who received carbetocin or misoprostol among women who had normal vaginal delivery. However, the hemoglobin levels were significantly reduced in misoprostol than carbetocin among females delivered by cesarean section [15]. In the same line, Attilakos *et al.* [16] compared carbetocin and oxytocin: the results were not significant different and there was no difference in the mean hemoglobin after delivery.

Furthermore, a study done by Fazel *et al.* [17], compared between rectal misoprostol and IV oxytocin and the results showed that the reduction in hemoglobin level in the two groups wasn't statistically significant [P = 0.55].

In current study, the amount of blood loss was significantly less in the Carbetocin group [364.79 ± 40.99 cc] than in misoprostol group [404.68 ± 67.24 cc] [p-value = 0.001]. This is coincided with the results done by Abd El Aziz *et al.* [15]; the results revealed that blood loss was significantly lower in carbetocin than misoprostol groups among females delivered through normal vaginal delivery [NVD] and those delivered by cesarean section.

In a study done by Mousa *et al.* [18] as they compared carbetocin, oxytocin and misoprostol; the mean blood loss was greater in the misoprostol than carbetocin group and the difference was statistically significant. Additionally, a recent research revealed that, blood loss was significantly lower in carbetocin than misoprostol among NVD as well as cesarean section groups [14].

This is in line with Khalafalah [19] as he found that the blood loss was 366.4 ±165 in the carbetocin group and was 434.7 ± 191.7 in the misoprostol group [p=0.01]. In another study done by Sallam and Shady [20], 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.

In the current study, the need for uterotonic drugs was affected by the type of drug used for prevention of PPH where the cases that had carbetocin as a prophylactic against PPH did not need additional uterotonic drugs [p-value = 0.003].

In a recent study, the researchers found that the need for additional uterotonics was significant between the groups. Their findings showed an increased use of additional oxytocics in the misoprostol group [32% of cases] versus [12% of cases] in carbetocin group [14]. This is in consistent with, Abd El-Wahab *et al.* [21], as the results showed that the need for other uterotonic drugs was less in carbetocin group than in misoprostol group as, nine of eighty cases needed additional uterotonic drugs in carbetocin group while in the misoprostol group twenty-five of eighty cases needed additional uterotonic drugs. Another randomized prospective study showed that the blood loss and the need for additional uterotonics were significantly lower with the use of carbetocin [22].

Ibrahim and Saad [23] performed prospective, randomized study and found that the need of extra-uterotonic drugs and need for blood transfusion was significantly higher with misoprostol than carbetocin. In the same line, Larciprete *et al.* [24] compared carbetocin and oxytocin in high- risk patients who underwent caesarean section and they noted that carbetocin was associated with lower use of additional uterotonics. In addition, Attilakos *et al.* [16] performed double-blind randomized study women at term undergoing elective or emergency caesarean section under spinal anesthesia; it was found that more women needed additional oxytocics in the oxytocin group significantly.

On the other hand, study by Elbohoty *et al.* [11] recorded no significant difference between carbetocin and misoprostol in the reduction of the risk of severe PPH. Also, Leung *et al.* [25] performed prospective, double-blinded, randomized study on women with a singleton pregnancy achieving vaginal delivery beyond 34-week gestation. The incidence of additional oxytocic injections was similar in the studied groups.

Regarding the need for blood transfusion the present study showed that it was not affected by the type of drug used. The above results were also noted by Maged *et al.* [22], as there was no significant difference between the carbetocin and oxytocin group regarding occurrence of major PPH, the need for blood transfusion. In addition, Attilakos *et al.* [16] researchers found that there were no significant differences in the secondary outcomes, including major PPH and blood transfusions. This is contrary to other results where the need for blood transfusion was found to be higher with misoprostol as compared to

carbetocin [23]. Also, Abd El-Wahab *et al.* [21] showed that the need for blood transfusion was different as in carbetocin group there wasn't any patient need blood transfusion versus 3 cases in misoprostol group need for blood transfusion.

In our research, the side effects showed heterogeneous results; some showed significance while others showed no difference. The cases that had side effects in the form of fever, nausea and vomiting, diarrhea and abdominal pain were found to be significant between misoprostol and carbetocin groups, where the cases in the carbetocin group were less likely to have these side effects after delivery. On the other hand, the cases that had adverse effects in the form of allergy, facial flushing and headache were found to be statistically not significant between misoprostol and carbetocin groups.

The results of different studies regarding side effects of drugs used to prevent PPH shows many conflicts and not consistent with each other. For instance, Abd El-Aziz *et al.* [15] stated that regarding side effects of drugs used to prevent PPH; the heart rate was higher in misoprostol than carbetocin. Additionally, the incidence of heat sensation, metallic taste, fever, and shivering were significantly higher in misoprostol than carbetocin. In addition, Su *et al.* [26] compared the effects of carbetocin to syntometrine and reported that side effects were more common in syntometrine than carbetocin.

Furthermore, Bellad *et al.* [27] performed double-blind randomized controlled trial consenting eligible pregnant females admitted to the labor room, and used sublingual misoprostol or oxytocin for prevention of PPH. Their results showed significantly lower side effects in the oxytocin than misoprostol group. Also, Ibrahim and Saad [23] reported the results regarding side effects, misoprostol was associated with shivering and pyrexia as compared to carbetocin while nausea, vomiting and headache were more associated with carbetocin.

A more recent study found that the side effects of drugs used to prevent PPH shows that abdominal pain, headache and tachycardia were more in carbetocin groups and the incidence of abdominal pain was less in misoprostol [21]. Another study presented by Leung *et al.* [25] clarified that the use of carbetocin was associated with significant lower incidence of nausea.

CONCLUSION

In conclusion, carbetocin was better than misoprostol for reducing postpartum blood loss in high-risk patients. It is associated with less use of additional uterotonic and fewer side effects. However, this conclusion should be cautiously

considered, as the assessment of PPH is usually a subjective matter and small sample size of patients were included irrespective of sample size justification.

Financial and Non-financial Relationships and Activities of Interest

None

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The cover art features a magnifying glass, a globe, and a stethoscope. The background is a light beige color with a faint, repeating pattern of ECG (heart rate) lines. The magnifying glass is positioned on the left side, with its handle extending towards the bottom. The globe is centered in the lower half of the image. The stethoscope is on the right side, with its chest piece resting on the globe. The overall color scheme is warm, with shades of beige, brown, and blue.

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