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ORIGINAL ARTICLE

Efficacy and Safety of Carbetocin in Prevention of Postpartum Hemorrhage

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ABSTRACT

Objective: The study compared the effectiveness of carbetocin and oxytocin, administered post caesarian section for prevention of postpartum haemorrhage (PPH).

Study Design: This was a prospective single center, case-control, cross sectional, observational, double ended study conducted from September 2020 to January 2022, comprising 150 female patients.

Methods: The study was conducted at Hameeda Memorial Hospital Lahore in women undergoing caesarean section under regional and general anesthesia. Women were randomized to receive either carbetocin or oxytocin 5 IU intravenously.

Results: Average age of patients was 34.5 years with average BMI of 27. It was noted that patients who were administered drugs had 348.6ml less blood loss than those not administered in PPH. Patients who did not received the drugs had average 800 ml blood loss. Whereas those who did had the drug had average of 451ml loss of bleed in PPH. Carbetocin showed effectiveness in preventing PPH by maintaining uterine tone. It was found that it significantly reduced the need for additional uterine contractile interventions to prevent or treat excessive bleeding after cesarean. In high-risk women, carbetocin has been found to be more effective than oxytocin in preventing blood loss greater than 500 mL during the cesarean section.

Practical Implication: This study will help the gynecologists in selecting potent and safe therapeutic agents for the prevention of postpartum hemorrhages in high risk females.

Conclusion: Carbetocin has been shown to be a safe and effective option for the prevention of postpartum hemorrhage in high-risk women as compared to other therapeutic agents along with potential safety margins.

Keywords: Carbetocin, efficacy, safety, prevention, postpartum hemorrhage, oxytocin, uterotonic

INTRODUCTION

Postpartum hemorrhage (PPH) is a significant obstetric complication and a leading cause of maternal morbidity and mortality worldwide. PPH is defined as excessive blood loss of 500 mL or more within 24 hours following childbirth. It can be classified into two categories: primary PPH, which occurs within the first 24 hours after delivery, and secondary PPH, which takes place between 24 hours and 12 weeks postpartum. The primary cause of PPH is uterine atony, a failure of the uterus to contract adequately after delivery. Other contributing factors include retained placental tissue, genital tract trauma, and coagulopathy[1].

The impact of PPH is particularly pronounced in low-resource settings, where access to quality obstetric care is limited and the risk of maternal death is significantly higher. Prompt recognition and timely management of PPH are crucial to improving maternal outcomes and preventing long-term complications. Current management strategies involve a combination of pharmacological interventions, mechanical methods, and surgical procedures. Uterotonic agents, such as oxytocin and misoprostol, play a pivotal role in the prevention and treatment of PPH by promoting uterine contractions and minimizing blood loss[2].

Despite global efforts to reduce the burden of PPH, its incidence remains high in both developed and developing countries. Continued research and innovation are necessary to identify novel strategies for PPH prevention, risk stratification, and management. In recent years, the focus has shifted towards the implementation of evidence-based guidelines and the evaluation of new pharmacological agents, such as carbetocin, as well as the development of low-cost, context-appropriate interventions that can be easily integrated into existing healthcare systems[3].

Carbetocin, a synthetic analogue of oxytocin, has emerged as a promising agent in the prevention of postpartum hemorrhage (PPH), a leading cause of maternal morbidity and mortality worldwide. PPH, defined as blood loss of 500 mL or more within 24 hours after childbirth, can lead to severe maternal complications and, in some cases, death. In low-resource settings, where access to timely and appropriate obstetric care is limited, the impact of PPH is particularly devastating. Over the past few decades, oxytocin has been the gold standard for prophylaxis and treatment of PPH, but its limitations, such as the need for cold storage and a short half-life, have driven the search for alternative pharmacological interventions. Carbetocin, an oxytocin receptor agonist, exhibits improved stability at room temperature and a longer half-life compared to oxytocin, making it a more suitable candidate for use in a variety of healthcare settings. Numerous clinical trials have investigated the safety and efficacy of carbetocin in preventing PPH, both as a standalone treatment and in combination with other uterotonic agents. Results have demonstrated the potential of carbetocin to significantly reduce the incidence and severity of PPH, thus improving maternal outcomes globally. This introduction will provide an overview of the current state of knowledge on carbetocin's role in PPH prevention, highlighting its pharmacological properties, clinical trial evidence, and potential applications in diverse obstetric settings[4].

Carbetocin is a long-acting synthetic analogue of oxytocin and is available as a single-dose injection. It can be given both intravenously and intra-muscularly. The half-life of intravenously administered carbetocin is approximately 40 minutes, Oxytocin has been reported. Effects of various IV injections Postpartum intramuscular administration of carbetocin into the uterus has been observed in 33 of 40 women 24 to 48 hours postpartum during contractions. Uterine activity lasted an average of 120 minutes after intramuscular injection and mean of 60 minutes after intravenous injection33. Thus, these information indicate that carbetocin's effects are rapid onset but of longer duration. Or the optimal dose of carbetocin (intravenous or intramuscular) is 100 [5,6,7].

Sufficient data on the efficacy and safety of carbetocin was not available in the literature; therefore, this study was conducted to investigate the efficacy and safety of carbetocin in prevention of postpartum hemorrhage.

METHODS

This is a prospective, single-center, case-control, two-tailed, cross-sectional, observational study conducted from September 2020 to January 2022 at the Department of Obstetrics and Gynecology, Hameda Memorial Hospital, Lahore. A total of 150 women

undergoing elective and emergency cesarean sections were consecutively enrolled for risk factors of postpartum hemorrhage, including fetal macrosomia, fetal malformations, and hypertension associated with polyhydramnios. Written informed consent was obtained from eligible women upon entry. Initially, the study enrolled 119 women who received Syntocinon (case group A), followed by 606 women who received Pabal (control group B). All patients received the same combined spinal epidural anesthesia (CSE). After administering this anesthesia, the subject was positioned, and an extremity cuff (Drager Infinity Delta®, Drager Medical Australia Pty Ltd) was applied for continuous blood pressure measurement. To assess the hemodynamic effects of carbetocin and oxytocin, blood pressure reduction was compared at 1, 3, and 5 minutes after drug administration during uterine healing while facing left during cesarean section. The study recorded signs of nausea, vomiting, hot flashes, headache, hypertension, and tachycardia.

The final conclusions of this study highlighted the requirement for additional uterotonics and the evaluation of decreased hemoglobin levels by comparing admission hemoglobin levels with measurements taken 2 and 24 hours postpartum. The bleeding was monitored immediately after the caesarean section and defined as excessive if it exceeded 1000 ml. Blood loss was estimated by the surgeon as per standard procedure. Blood pressure (mmHg), uterine tone (classified as excellent, good, adequate, or atony), and uterine position (measured at the umbilical point) were recorded 2 hours, 12 hours, and 24 hours after delivery by the same midwife. All patients were given a Foley catheter and kept in place for 24 hours after the cesarean section, and urine output was monitored 2 hours and 12 hours after delivery by a midwife.

Carbetocin in Caesarean Delivery: Carbetocin is presently authorised in 23 countries for the prevention of uterine atony and excessive bleeding at some stage in spinal or epidural caesarean segment. This healing indication is supported via the effects of two published managed scientific research[8, 9]. The first observe, performed at Hameda Memorial clinic, Lahore, turned into an attitude, randomized, case-manipulate, pass-sectional, observational, double-ended, examine-controlled look at. Comparison of uterotonic effects and protection of carbetocin and oxytocin in 785 girls undergoing elective caesarean section35. Her single intravenous injection of one hundred µg carbetocin after transport of the placenta become as a minimum as powerful in controlling blood loss in the course of surgery as her sixteen-hour intravenous injection of 32.five IU oxytocin. No enormous differences in mean blood loss had been located among remedy organizations. However, extensively fewer girls lost extra than 200 mL of blood within the carbetocin institution (fifty three %) than within the oxytocin organization (p = zero.041). information from these treatments have been discovered. The risk of postpartum hemorrhage, described as blood lack of 500 mL or extra, was not extensively reduced with carbetocin compared with oxytocin (relative hazard [RR] = 0.71 and ninety five% confidence c program languageperiod [CI] = 0.14-3.53). However, carbetocin notably decreased the want for subsequent intervention with uterotonics (RR = zero.forty four, 95% CI = 0.25-0.78) OR Uterine rub down as compared with oxytocin (RR = 0.38, 95% CI = 0.18-zero.80). Authors 29 additionally evaluated 37 published abstracts of randomized managed trials that in comparison an unmarried intravenous injection of 100 µg carbetocin (n=62) with placebo (n=fifty seven). Optionally available caesarean segment. despite the fact that the occurrence of postpartum haemorrhage could not be assessed, extra oxytocin therapy to prevent bleeding turned into appreciably much less with carbetocin than with placebo (RR = 0.18, ninety five% CI = 0.09-0.35). Additionally, the female in the carbetocin organization had a sizeable weight benefit in her 20 mins. Investigational drug management vs placebo (p < 0> _ 500 mL determined most effective in ladies receiving oxytocin[9].

Effectiveness in Caesarian Delivery: At some point of those activities, 10% of women pronounced experiencing headache, tremor, hypotension, flushing, nausea, stomach ache, itching and nausea of warmth. Within the check assessment Carbetocin vs placebo, warm flashes, belly pain, and pruritus have been moe often discovered with carbetocin it turned into also related to hypotension and transient tachycardia[10]. Destructive occasions observed in research of carbetocin as opposed to oxytocin have been comparable in kind and frequency among remedies, and analyzes of those studies were consistent The risks of headache, tremor, dizziness, flushing, shortness of breath, premature ventricular contraction/tachycardia, stomach ache, nausea, vomiting, metal flavor, itching, back pain, heat sensation, chills, and sweating have been similar. Carbetocin or Oxytocin[11].

RESULTS AND DISCUSSIONS

150 patients were taken for study. Their average age was 34.5+9.86 years. Their average BMI was 27. 45.33% of the participants were educated and 14% also had history of abortion (Table 1). 100 were introduced to the drug ad 50 were not (Table 2). It was recorded that those who were introduced to the drugs had 348.6ml less blood loss to those who did not had the drug in pph. Those who did not had received the drug had average 800 ml blood loss. Whereas those who did had the drug had average of 451ml loss of blood in pph (Table 3). Postpartum hemorrhage (PPH) is a leading cause of maternal morbidity and mortality worldwide. It is defined as a loss of more than 500 mL of blood after delivery and is a significant contributor to maternal death in developing countries. Uterotonic drugs, such as oxytocin and ergometrine, have been used to prevent PPH, but they have limitations such as short duration of action and adverse side effects.

Carbetocin, a long-acting artificial analogue of oxytocin, has been shown to be effective in preventing PPH by maintaining uterine tone. Carbetocin has been compared to both placebo and intravenous oxytocin in randomized controlled trials and has been found to significantly reduce the need for additional uterine contractile interventions to prevent or treat excessive bleeding after cesarean. In high-risk women, carbetocin has been found to be more effective than oxytocin in preventing blood loss greater than 500 mL during the cesarean section.

In addition to its efficacy, carbetocin has a similar tolerability profile to intravenous oxytocin, with a lower occurrence of gastrointestinal side effects compared to the combination of oxytocin and ergometrine. However, a higher occurrence of tachycardia has been reported with carbetocin compared to syntometrine. The length of tachycardia was not reported, but based on available data from other studies, the transient, modest increase is not clinically significant and is expected to be within the normal range of 100-120 beats/minute during pregnancy[12, 13].

Despite its potential benefits, the use of carbetocin is not without limitations. Pre-eclampsia remains a contraindication to carbetocin use, and close monitoring of blood pressure is necessary for patients with suspected pre-existing cardiovascular disease. The cardiovascular side effect profile of carbetocin requires further research, as does its efficacy and safety in low-risk women and in other therapeutic settings[14].

In conclusion, carbetocin has been shown to be a safe and effective option for the prevention of postpartum hemorrhage in high-risk women. Further studies are needed to determine its efficacy and safety in low-risk women and in other therapeutic settings. Health care providers should be aware of the limitations and potential side effects of carbetocin when making treatment decisions for patients.

Table 1: Demographic data of study patients

S.No	Variable	Value
1	No. of patients (n)	150
2	Age (Mean+SD) years	34.5+9.86
3	BMI	27
4	Educated n(%)	68 (45.33)
5	History of abortion	21 (14)

Table 2: Stratification of patients into study groups.

S. No	Group	Drug administered	Remarks
1	A	Carbetocin	Treatment group
2	B	Oxytocin	Treatment group
3	C	Placebo	Control group

Table 3: Blood loss in PPH in study patients

S. No	Group	Blood Loss (PPH)
1	A	348.6 ml
2	B	451.18 ml
3	C	800.98 ml

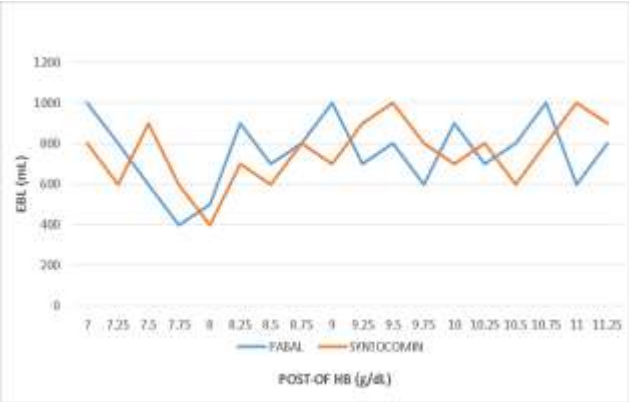

Fig.1: In first graph the loss of HB level after caesarean section was high when the pabal gave to patient. As compare to syntocomin level was low estimated.

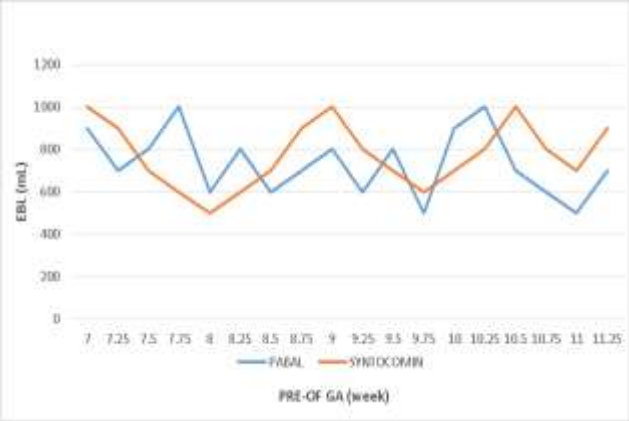

Fig. 2: According to studies the gestation level was high in syntocomin group before delivery. As compare to pabal the level was low estimated.

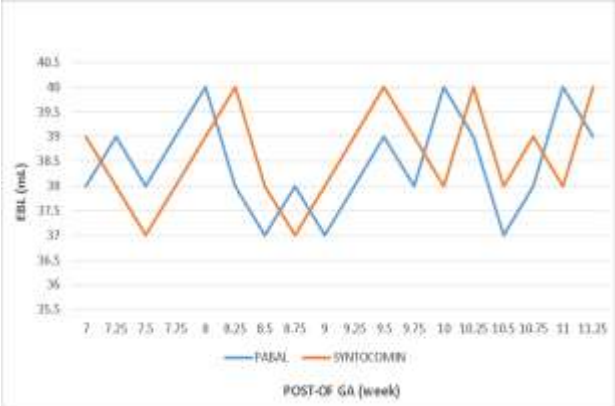

Fig. 3: According to research gestation was estimated high in syntocomin group as compare to pabal group after caesarean section.

CONCLUSION

Carbetocin, a long-acting artificial analog of oxytocin that combines the safety and tolerability of oxytocin with the sustained uterotonic activity of ergometrine, is currently indicated for the prevention of post-cesarean uterine atony. Based on two randomized controlled trials, a single injection of 100 µg carbetocin maintains uterine tone and significantly reduces the need for additional uterine contractile interventions to prevent or treat excessive bleeding after cesarean compared to placebo or intravenous oxytocin. Furthermore, the use of a single carbetocin injection is more effective than oxytocin infusion. In high-risk women, carbetocin is more effective than oxytocin and can prevent blood loss greater than 500 mL during the cesarean section. Results from recent clinical trials suggest that it may be the most cost-effective uterotonic agent in resource-poor developing countries. In Bahrain, associated randomized controlled clinical trials and studies show that carbetocin is a superior alternative to traditional uterotonic drugs for preventing postpartum hemorrhage after delivery.

Carbetocin demonstrated a longer duration of action when given as a single dose of 100 µg compared to intravenous oxytocin. In low-risk women, carbetocin is at least as effective as syntometrine. Carbetocin has a similar tolerability profile to intravenous oxytocin, with a lower occurrence of gastrointestinal side effects compared to the combination of oxytocin and ergometrine. However, a higher occurrence of tachycardia was reported with carbetocin compared to syntometrine. Although the length of tachycardia was not reported, based on available data from other studies, the transient, modest increase is not clinically significant and is expected to be within the normal range of 100-120 beats/minute during pregnancy.

Carbetocin has a better cardiovascular side effect profile than oxytocin and syntometrine, but the available data from the published literature is limited. Further research is needed to examine the effect of carbetocin on blood pressure. Pre-eclampsia remains a contraindication to carbetocin use and careful collection of the patient's medical history and close blood pressure monitoring is necessary for patients with suspected pre-existing cardiovascular disease.

These studies suggest that carbetocin is potentially effective for postpartum bleeding in high-risk women. Further studies in low-risk women in labor are needed to determine if carbetocin is superior to other uterotonics for most pregnant women. Additionally, research can be done to examine if intramuscular administration of carbetocin is useful in therapeutic settings where prophylactic use of intravenous uterotonics is hazardous or impractical, such as primary care clinics and level 3 obstetrics in developing nations.

Suggestions and Recommendations: Based on the available evidence, the following are some suggestions and recommendations for the efficacy and safety of carbetocin in the prevention of postpartum hemorrhage:

1. Carbetocin should be considered as a first-line option for the prevention of postpartum hemorrhage in high-risk women, as it has been shown to be more effective than oxytocin and syntometrine.
2. Carbetocin may also be a cost-effective alternative to traditional uterotonic drugs for preventing postpartum hemorrhage in resource-poor developing countries.
3. Close monitoring of blood pressure is necessary for patients with suspected pre-existing cardiovascular disease, as pre-eclampsia remains a contraindication to carbetocin use.
4. Further studies in low-risk women in labor are needed to determine if carbetocin is superior to other uterotonics for most pregnant women.
5. Intramuscular administration of carbetocin should be further studied as a potential alternative to intravenous administration in therapeutic settings where prophylactic use of intravenous uterotonics is hazardous or impractical.
6. Health care providers should be aware of the higher occurrence of tachycardia with carbetocin compared to syntometrine, but the transient, modest increase is not clinically

significant and is expected to be within the normal range of 100-120 beats/minute during pregnancy.

7. The gastrointestinal side effect profile of carbetocin is lower compared to the combination of oxytocin and ergometrine, but the cardiovascular side effect profile of carbetocin requires further research.

In conclusion, carbetocin should be considered as a safe and effective option for the prevention of postpartum hemorrhage in high-risk women, and further studies are needed to determine its efficacy and safety in low-risk women and in other therapeutic settings.

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