

# Clinical Study on Role and Efficacy of Lower Dose of Carboprost [125 µg] and its Comparison with Oxytocin [10 Units] in Prevention of Postpartum Haemorrhage in Caesarean Section

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## Abstract

## Original Research Article

**Introduction:** Post-partum hemorrhage (PPH) is an important cause of maternal mortality accounting for nearly 25% of maternal deaths worldwide. It is reported to occur in ~4-6% of all deliveries, and the risk is significantly greater with caesarean delivery than vaginal delivery. Oxytocin is universally accepted as drug of choice but carboprost has also been found to be effective in management of third stage of labour. Carboprost 250 microgram (µg) is associated with significant side effects; however its lesser dose may prove a better uterotonic with fewer side effects. **Aims and objective:** To evaluate the role and scope of using prophylactic intramuscular carboprost [125 µg] in comparison with intramuscular oxytocin [10 units] in prevention of PPH in caesarean section. **Material and methods:** 200 pregnant women admitted in labour room undergoing caesarean section were included in this study after taking informed consent and were randomly divided into group 1 and 2, where Group 1 received intramuscular carboprost 125 microgram and Group 2 received intramuscular oxytocin 10 units, within 1 min of delivery of baby. Comparative study was done in both the groups and assessment was done in terms of blood loss, incidence of PPH, additional requirement of drugs and side effects. **Results and conclusion:** Patients who received carboprost [125 µg] had lesser blood loss as compared to patients who received oxytocin. Mean blood loss was 405 ml and 560 ml in patients who received carboprost and oxytocin respectively. Also there was less need of additional uterotonics in patients who were given carboprost. Out of 50 patients receiving carboprost only 4 patients complained of vomiting and 8 complained of nausea.

**Keywords:** Carboprost, Oxytocin, Post-partum hemorrhage.

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## INTRODUCTION

About 830 women die from various complications related to pregnancy and childbirth everyday [1]. The MMR in developing countries in 2015 was 239 per 100,000 live births as compared to 12 per 100,000 live births in developed countries [2]. Thus, 99% of maternal deaths occur in developing countries. Only 1% of maternal deaths occur in developed world. As per literature, 52% of maternal deaths are attributed to three leading cause- sepsis, hypertension and haemorrhage, all of which are preventable [3]. Post-partum hemorrhage (PPH) affects maternal health in a very adverse way and causes morbidity and mortality but is a very highly preventable condition. WHO statistics show that 25% of maternal deaths are due to PPH. Out of the above three, PPH is the quickest killer, can kill a healthy female within hours if not treated. In India, a sample registration scheme [SRS] survey in 1998 showed that PPH was a major cause of maternal death and accounted for 30% of

all maternal mortality, which increased to 38% according to SRS 2001-2003 [4].

The definition of PPH is arbitrary and is related to amount of blood loss in excess of 500 ml following birth of baby. However, the average blood loss during vaginal delivery, caesarean delivery and caesarean hysterectomy is 500 ml, 1000 ml and 1500 ml respectively [5]. Postpartum haemorrhage (PPH) can be classified as primary (early) or secondary (late). Primary Postpartum haemorrhage is traditionally defined as loss of more than 500ml of blood from genital tract at vaginal delivery, 1000ml at caesarean section or 1500 ml at caesarean hysterectomy, but the Definition of PPH based on just the amount of blood is not sufficient, especially in a country like India where women are already anemic. Also danger of PPH depends not only on amount of blood loss but also on rate at which it is lost. Thus, a lower value of 300ml of blood loss has been suggested as

a cut off for Asian women because of their lower Body mass index [6]. Thus clinical definition of PPH is “Any amount of bleeding from or into genital tract following birth of the baby up to the end of the puerperium, which adversely affects the general condition of the patient evidenced by rise in pulse rate and falling blood pressure is called postpartum haemorrhage [5]”. Alternative definition includes a drop in 10% of haematocrit or the need of blood transfusion within first 24 hours of delivery [6]. Secondary PPH occurs 24 hours to 6 weeks after delivery. Most cases of morbidity and mortality due to PPH are the result of primary PPH, while secondary PPH results from retained placenta (bleeding diatheses) which causes abnormal excessive fragments, subinvolution of the placental site, infection, and coagulation defects bleeding. It is the primary postpartum haemorrhage that we are mainly concerned with as it may convert a normal delivery to a disaster. PPH is reported to occur in ~4% of vaginal deliveries, and the risk is significantly greater with caesarean delivery [6%] than vaginal delivery [6].

The majority of maternal deaths due to PPH may be avoided, and the key lies in early diagnosis and proper treatment. Active management of the third Stage of labor (AMTSL) is universal for both vaginal delivery and caesarean section. It includes administration of uterotonic agents [oxytocin 10 units IM], within 1 Minute of delivery of baby, uterine massage and Controlled cord traction [Brandt-Andrews technique].

There are various drugs and methods available for management of PPH. Drugs like oxytocin, ergot alkaloids, and various prostaglandins can be used for the management of third stage of labour. Oxytocin is the most commonly used uterotonic agent for the prevention of PPH and has been demonstrated to reduce blood loss following delivery. It has been used for more than 50 years to treat uterine atony with bleeding. It has almost no contraindications and can be used in high risk cases such as anemia, pre-eclampsia, eclampsia. However, oxytocin has a half-life of <10 min and therefore should be administered by continuous intravenous infusion. Furthermore, saturation of uterine receptors may occur, and excessive dosages are capable of producing water toxicity due to its antidiuretic effect [in high doses]. Also there is need for cold chain maintenance in absence of which its effectiveness is reduced. So, there was need to find alternative drug. Other uterotonic agents have been studied, and have been shown to reduce PPH, including ergot alkaloids and prostaglandins (such as misoprostol and carboprost 250 microgram ( $\mu\text{g}$ ) IM and carbetocin.

Prostaglandins and their analogues have been used for management of PPH not controlled by oxytocin alone. These are effective in increasing uterine tone and have got longer duration of action as compared to oxytocin and even ergometrine. In prostaglandins, two

alternatives are available misoprostol [PGE1] and carboprost [PGF2 $\alpha$ ].

Carboprost was approved 25 years ago for uterine atony treatment in a dose of 250 microgram [250  $\mu\text{g}$ ] given intramuscularly (IM). This dose can be repeated if necessary at 15-90 minute interval up to maximum of eight doses. At present, it is available in two doses-250  $\mu\text{g}$  and 125  $\mu\text{g}$ . Carboprost is associated with more side effects when used in dose of 250  $\mu\text{g}$ . There are various studies comparing different classes of drugs. Only few studies are done where carboprost is compared with other drugs like methylergometrine and syntometrine [combination of oxytocin and ergometrine and was found better uterotonic drug [7-14]. It is a physiological stimulant of myometrial activity. It can be used when methylergometrine is contraindicated. It has been found to be effective in patients with high hemorrhagic risk factors including twin pregnancy, severe pre-eclampsia, eclampsia, polyhydramnios, fetal macrosomia, placenta previa. When carboprost is used in 125  $\mu\text{g}$ , it may be associated with lesser side effects.

Carboprost is found to be better uterotonic drug but the only concern was high dosage and side effects associated with it. With carboprost 125  $\mu\text{g}$  it may prove to be the better drug for third stage of labour with fewer side effects.

## AIMS AND OBJECTIVES

The study was undertaken to evaluate the role and scope of using prophylactic intramuscular carboprost [125  $\mu\text{g}$ ] in comparison with intramuscular oxytocin [10 units]. The study also aimed to know the clinical efficacy, safety and cost effectiveness of both drugs.

## MATERIALS AND METHODS

The study included 200 pregnant women admitted in labour room undergoing caesarean section at Rajendra Institute of Medical Sciences, Ranchi, during a period from September 2017 to August 2018. Patients with hypersensitivity to drugs, respiratory diseases (asthma), liver disorder, severe cardiovascular disease, renal disease, history of bleeding disorder were excluded from the study. Written informed consent was taken from all patients enrolled in the study. They were evaluated by history, clinical examination and relevant investigations. All 200 cases were randomly divided into two groups. Comparisons were made in terms of clinical and quantitative assessment of blood loss, incidence of PPH, additional requirement of drugs, side effects, and efficacy.

## OBSERVATIONS AND RESULTS

A total of 200 pregnant women who underwent caesarean section (CS) were included in this study. There were 100 cases in each group. Group 1 included patient receiving Carboprost and Group 2 included patient with oxytocin.

Patients were between 18 to 40 years of age and gestational age was between 5 to 40 weeks. No significant difference was identified in maternal age, gravida, parity and reasons for CS in both groups. Age distribution in both groups was similar. Maximum patients in both groups were in age group 21-25 years. In group 1, 53% and in group 2, 48% were from age group 21-25 years. In group 1, 25% patients were para2-5 and in group 2, 22% patients were para2-5. Most of the patients were either nullipara or primipara. 73% of cases had emergency CS in group 1 as compared to 67% in group 2. Thus; most of the cases in our study were emergency CS.

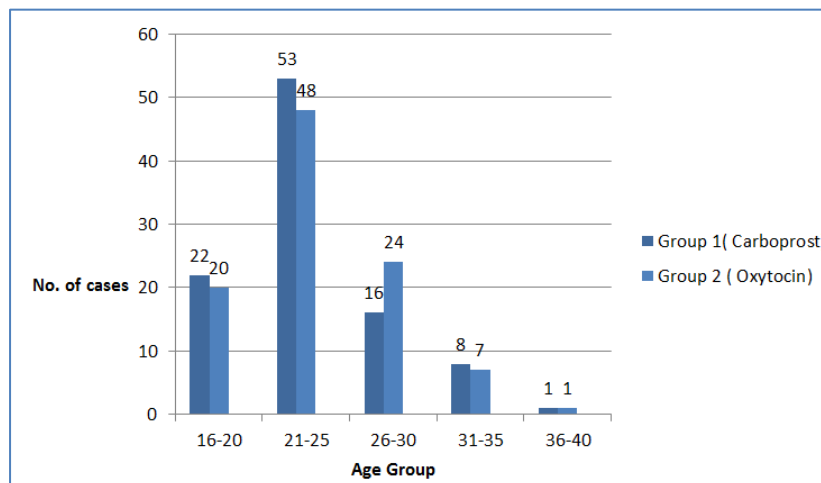
In Carboprost group, mean blood loss was 470.55 ±196.32ml. In Oxytocin group, mean blood was 578.80 ml ±244.45 ml. The difference between mean blood losses in two groups was 108.35 ml.

In group 1, 70% cases had blood loss <500 ml. 23% had blood loss between 500- 999ml whereas in group 2, 49% patients had blood loss <500ml and 45% cases had blood loss between 500-999ml. 6% had blood loss >1000ml [Figure 3].

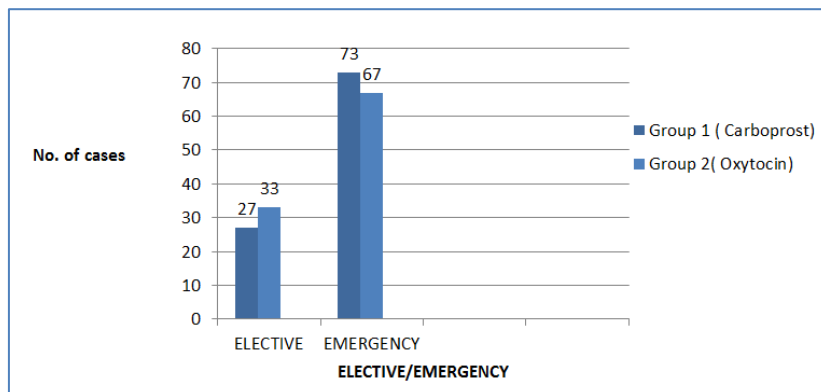
Additional uterotonics were used at the earliest sign of increased blood loss. We did not wait for blood loss to increase upto 1000 ml [which is the quantitative definition of PPH in CS] because most patients in our study were already anemic and therefore the usual quantitative definition of should not be applied in these cases. Additional uterotonics were required in 30% cases in oxytocin group whereas in carboprost group 17% cases needed additional drugs [Figure 4].

Nausea and diarrhea were the most common side effects seen in both the groups but incidence was higher in carboprost group. Diarrhoea was the only significant side effect with carboprost. Rest all were comparable to side effects seen in oxytocin group [Figure 5].

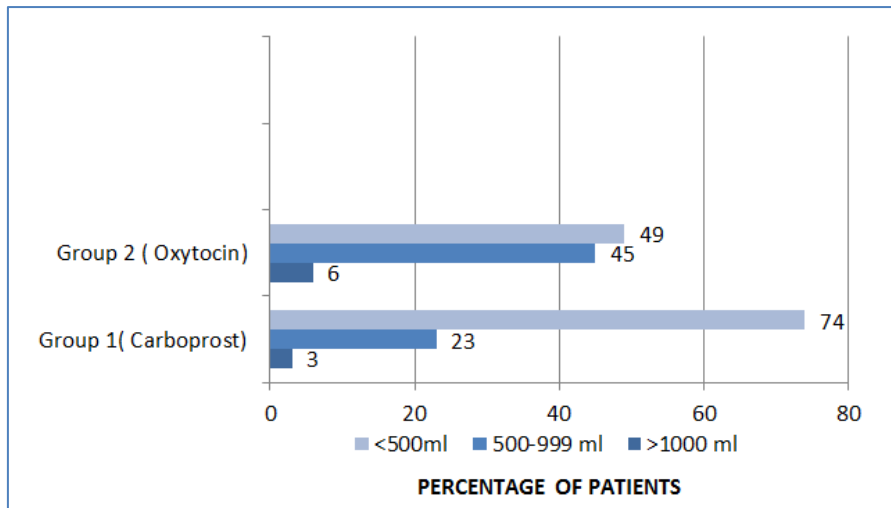
Most side effects were seen when higher dose [250 mcg] of carboprost or additional uterotonics were used. Mean difference of haemoglobin before and after CS in group I was 1.02 ± 0.592 whereas in group II, the difference was 1.37 ±0.763. P value is <0.001, which is significant.



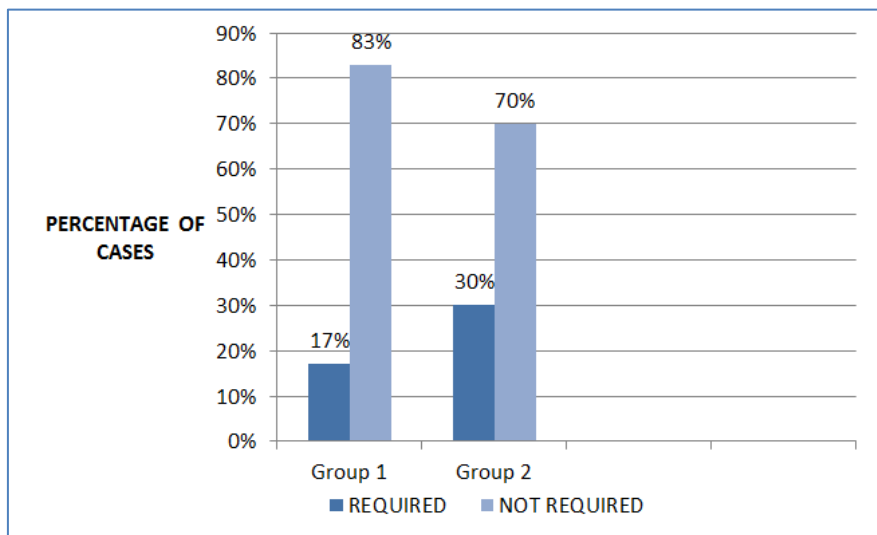
**Fig-1: Showing Distribution of Cases According to Age**



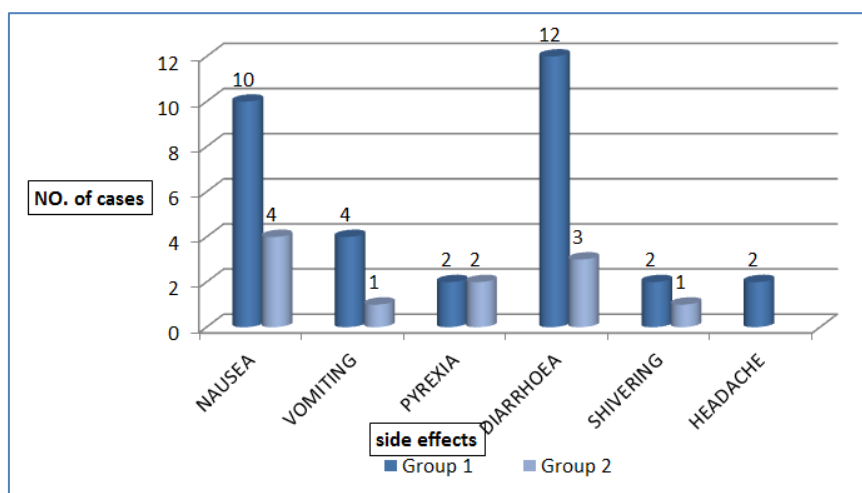
**Fig-2: Distribution according to elective/emergency cs**



**Fig-3: Comparison of blood loss in both groups**



**Fig-4: Additional uterotonics required**



**Fig-5: Side effects**

**DISCUSSION**

Third stage of labour is a very crucial stage and if not paid attention may lead an uneventful pregnancy into a disastrous one. PPH is a major cause of morbidity

and mortality. At present many oxytocics are in use like oxytocin, misoprostol, carbocetin, methylergometrine and carboprost. But it is necessary to evaluate the effectiveness of these drugs specially when used alone.

Aim of this study was to evaluate the role and scope of using prophylactic intramuscular carboprost in a lower dose [125 µg] in comparison with intramuscular oxytocin [10 units] in prevention of PPH in patients undergoing caesarean delivery. 200 pregnant women admitted in labour room undergoing caesarean section were included in this study and they were randomly divided into group 1 and 2, where Group 1 received I.M carboprost 125 µg and Group 2 received I.M oxytocin 10 units, within 1 min of delivery of baby. Comparative study was done in both the groups and assessment was done in terms of blood loss, incidence of PPH, additional requirement of drugs and side effects.

Age distribution in both groups was similar. Maximum patients in both groups were in age group 21-25 years. In group 1, 53% patients and in group 2 48% were from age group 21-25 years [Figure 1]. In group 1, 25% patients were para 2-5 and in group 2, 22% patients were para 2-5. Most of the patients were either nullipara or primipara showing that nowadays most people prefer small family. 73% of cases had emergency CS in group 1 as compared to 67% in group 2. Thus, most of the cases in our study were emergency CS [Figure 2]. In Carboprost group, mean blood loss was  $470.55 \pm 196.32$  ml. In Oxytocin group, mean blood loss was  $578.80 \pm 244.45$  ml. The difference between mean blood losses in two groups was 108.35 ml. The difference in blood loss is significant as  $P < 0.05$ . The standard error of difference is 19.63 in carboprost group and 24.44 in oxytocin group.

In study by Jing bai *et al.* [2014], median blood loss in oxytocin, carboprost and oxytocin plus carboprost groups were 610 ml, 438 ml, 520 ml respectively, showing blood loss was higher where only oxytocin was used [8]. Another study by K.S. Sunil Kumar *et al.* [2016] in which they compared oxytocin [10 units] and carboprost [125 µg] in management of third stage of labour showed that patients who received carboprost had significant reduction in both duration of 3<sup>rd</sup> stage of labour as well as mean blood loss [9].

In our study, in group 1, 70% cases had blood loss <500 ml. 23% had blood loss between 500-999 ml whereas in group 2, 49% patients had blood loss <500ml and 45% cases had blood loss between 500-999 ml. Six percent patients had blood loss >1000ml in those who received oxytocin whereas the number was much lower in those who received carboprost. Nausea and diarrhea were the most common side effects seen in both the groups but incidence was higher in carboprost group. Diarrhoea was the only significant side effect in carboprost. In a study by Lamont *et al.*, on efficacy and safety of an analogue of 15-PGF<sub>2</sub> alpha and its comparison with syntometrine in prevention of postpartum haemorrhage, they reported that diarrhoea was significantly more in PGF<sub>2</sub>α [10]. Most side effects were seen when higher dose [250 µg] of carboprost or additional uterotonics were used. Mean difference of

haemoglobin before and after CS in group 1 was  $1.02 \pm 0.592$  whereas in group 2, the difference was  $1.37 \pm 0.763$ . P value is <0.001, which is significant. Study by Wu LF *et al.* on use of hembat [carboprost] in caesarean section showed that hembat significantly reduce haemorrhage in women with high haemorrhagic risk factors and can be used as first line drug along with oxytocin during and after CS [11].

## CONCLUSION

Postpartum haemorrhage remains leading cause of maternal mortality and morbidity worldwide. Oxytocin is the drug of choice for acute management of third stage of labour. Our study showed that carboprost effectively reduced mean blood loss [ $p < 0.01$ ]. The number of patients requiring additional uterotonics in oxytocin group was more (30%) as compared to carboprost (17%), which is statistically significant ( $p < 0.01$ ). Although the initial cost of carboprost 125 µg is three times the price of oxytocin but the number of patients requiring additional uterotonics was much higher which would result in higher expenditure. There is decreased need of blood transfusion as there is lesser blood loss in carboprost group. However more number of studies and on a larger scale, are needed to further confirm the results.

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