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CORBOPROST VERSUS OXYTOCIN FOR ACTIVE MANAGEMENT OF THIRD STAGE OF LABOR : A PROSPECTIVE RANDOMIZED CONTROL STUDY

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ABSTRACT **Background and Objectives:** Postpartum hemorrhage is the single largest and leading cause of maternal morbidity and mortality not only in developing countries but also in developed countries. The present study is an attempt to evaluate the scope of using prophylactic intramuscular carboprost tromethamine 125 µg in comparison with intramuscular oxytocin 10 units for the active management of third stage of labor. **Materials and Methods:** 120 pregnant women at term with spontaneous onset of labor were included in the study and were randomly divided into 2 groups of 60 women each. Group A and group B were given injection oxytocin 10 units and injection carboprost tromethamine 125 µg intramuscularly, respectively, at the time of delivery of anterior shoulder. The main outcome measures with respect to third stage of labor were: duration, blood loss by volume, difference in hemoglobin, need for additional oxytocics and side effects. **Results:** Subjects who received carboprost tromethamine 125 µg showed a significant reduction in duration of third stage of labor ($p < 0.05$) and blood loss ($p < 0.01$) when compared to the subjects who received oxytocin 10 units. Likelihood of occurrence of postpartum hemorrhage was reduced without significant side effects except for diarrhea. Additional need for other uterotonics after carboprost was significantly less compared to oxytocin. **Conclusion:** Intramuscular carboprost 125 µg is a better cost-effective alternative as compared to 10 units intramuscular oxytocin in active management of third stage of labor.

KEYWORDS : Active management of third stage of labor; Brasss V drape; Carboprost; Oxytocin; Postpartum hemorrhage; Third stage of labor.

INTRODUCTION

The third stage of labor is the most crucial stage, which begins with expulsion of baby and ends with expulsion of placenta and membranes. Its average duration is 15 min in both primigravida and multigravida [1]. Postpartum hemorrhage (PPH) is one of the dreaded complications of third stage of labor. Maternal mortality rate in India is 122 per 100,000 live births. Among these, 30 % of deaths are due to postpartum hemorrhage [3].

Routine active management of third stage of labor could play an important role in reducing maternal mortality and morbidity due to PPH in modern obstetrics. The decrease in problems associated with third stage of labor has been attributed to judicious use of different oxytocic preparations administered at time of delivery of anterior shoulder and a transition from expectant to active intervention [4, 5].

Drugs conventionally used for prophylaxis against PPH include oxytocin, methyl ergometrine, 15 methyl PGF2α (carboprost) and syntometrine (combination of ergometrine and oxytocin) [6]. Recent studies have shown that globally there are still wide variations in practice in the management of third stage of labor [7, 8]. Prophylactic use of uterotonics after delivery of the infant has been shown to reduce the incidence of PPH by 40 %. But it is associated with side effects ranging from nausea, vomiting and hypertension to rarely, postpartum eclampsia, intracerebral hemorrhage, myocardial infarction, cardiac arrest and pulmonary edema [2].

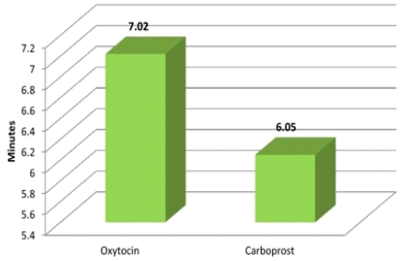

Fig-1: Mean duration of third stage of labour

Carboprost tromethamine is a 15 methyl PGF2α analogue, given as a single intramuscular injection in prophylactic dose (125 µg) for prevention of PPH, has lesser side effects than carboprost at therapeutic dose and is free from side effects such as hypertension and pulmonary edema compared to other uterotonics [9]. The present study is an attempt to evaluate the scope of using carboprost tromethamine 125 µg which is half the therapeutic dose for PPH and to evaluate its efficacy in terms of amount of blood loss, duration of third stage, side effects in comparison with oxytocin 10 units in active management of third stage of labor (Fig. 1).

METHODOLOGY

This prospective study was conducted at AIMS kankamamidi village moinabad mandal ,RR dist. During a one year period from April 2019 to March 2020. Ethical clearance for the study was taken from the hospital ethical committee. Informed consent was taken from patients after explaining the study in her own language, using a standardized form after admission to the labor ward. Women who were likely to have vaginal delivery were offered entry to the trial with a random assignment using serially numbered sealed envelopes, to either control group to receive intramuscular oxytocin 10 units (group A) or to the study group to receive intramuscular carboprost tromethamine 125 µg (group B). All women admitted in labor beyond the period of viability were offered participation in the study. Women with hypersensitivity to drugs, asthma, cardiac diseases, epilepsy, psychiatric disorders, liver and renal diseases were excluded from the study. Women who failed to achieve vaginal delivery were also excluded.

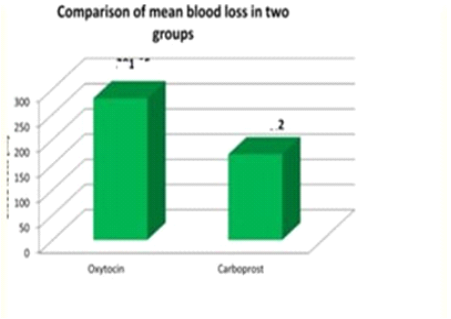

Fig-2: Comparison of mean blood loss in two groups

This study was performed on 120 women with 60 in each group. After recruitment and informed consent, hemoglobin estimation was done. Patients assigned to group A received 10 units oxytocin intramuscularly and group B received carboprost 125 µg intramuscularly at the time of delivery of anterior shoulder of baby or as soon as feasible after delivery. Perineal drapes were replaced by calibrated Brasss V obstetric drape after the delivery of the baby. The average time taken for episiotomy suturing was around 10 min in both the groups and did not have any significant impact on the blood loss and duration of bleeding. Brasss V drape was removed 10 min after the episiotomy suturing in all patients unless the patient continued to have significant PPH. Patients were further monitored for 2 h postpartum for PPH and side effects of the drug (Fig. 3).

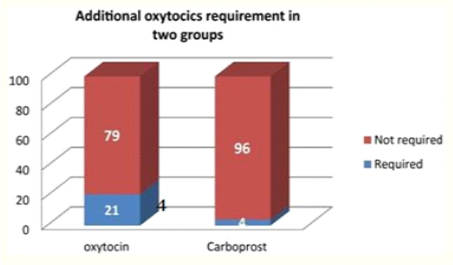

Fig-3: Additional oxytocics requirement in two groups

The duration of third stage of labor, amount of blood loss, need for additional uterotonics, complications and side effects were recorded. If a woman had significant blood loss, then usual hospital protocol for management of PPH was followed. This included uterine massage, use of additional oxytocin or methyl ergometrine, or carboprost 250 µg or misoprostol, looking for the lacerations, exploring the uterus for retained products and blood transfusion if required. Hemoglobin was sent 24 h after delivery for all the patients.

STATISTICALANALYSIS

Data were entered into Microsoft Excel® and analyzed using open source R statistical software package version 3.0.2. The distribution of data was tested using Shapiro–Wilk test, which showed that data would normally distribute in all the groups. Data were summarized as mean and proportion. Unpaired t test was used to test the difference between the two different groups. Paired data were analyzed using paired t test. Chi-square test was used to analyze the difference in proportions, and p values are reported accordingly. The primary outcome was considered significant if p value is <0.05.

RESULTS

A total of 120 women were enrolled in the study with 60 in each group. Patients assigned to group A received 10 units oxytocin intramuscularly and group B received carboprost tromethamine 125 µg intramuscularly at the time of delivery of anterior shoulder of baby for the active management of third stage of labor. Descriptive statistical tools like mean and proportion were used to calculate data. Student's t test and Chi-square test were used to compare the efficacy of two drugs.

There was no significant difference between the groups with respect to age, parity, gestational age, birth weight of the babies, episiotomy and vaginal or cervical lacerations (Table 1). Parity ranged from 0 to 5 in group A and 0 to 4 in group B. There was only one grand multipara (parity ≥ 5) in the entire study who was enrolled in group A.

Table 1: Demographic characteristics

	Group A (oxytocin)	Group B (carboprost)
Mean maternal age in years	22.78 ± 2.8	22.5 ± 2.8
Parity	1	1
Mean gestational age in weeks	38.1	37.5
Mean hemoglobin prior to delivery in g/dl	9.68 ± 1.39	9.75 ± 1.2
Mean birth weight in grams	2566	2655
Episiotomy in percentage	63	58
Cervical/vaginal lacerations in percentage	5	6

Table 3 shows the outcome of third stage of labor. The mean duration of third stage of labor in oxytocin group was 7.02 ± 2.6 min, and in carboprost group, it was 6.05 ± 1.7 min, which is statistically significant ($p < 0.001$). The majority of subjects (85 %) in oxytocin group had blood loss of more than 200 ml, whereas in carboprost group majority (75 %) had <200 ml. The mean blood loss between the groups showed a statistically significant difference, and the mean difference was 110 ml ($p < 0.01$, $t = 11.24$). The number of patients requiring additional uterotonics in oxytocin group was more (21 %) compared to carboprost group (4 %), which is statistically significant ($p < 0.01$). Additional oxytocics in the form of methylergometrine 0.2 mg, misoprostol (PGE1) 800–1000 µg or carboprost 250 µg were provided. This difference was statistically significant. Although the initial cost of carboprost 125 µg is double the amount of oxytocin, the number of patients requiring additional uterotonics in oxytocin group was much higher as shown in our study which would result in additional expenditure. Hence, overall carboprost 125 µg is cost-effective compared to oxytocin in the prophylaxis of PPH.

Table 3 : Outcome of third stage of labor

	Group A (oxytocin)	Group B (carboprost)	Statistical analysis
Mean duration of third stage in minutes	7.02	6.05	t = 3.12, p = 0.002
Mean blood loss (ml)	281.05	170.2	t = 11.24, p < 0.0001
Additional use of uterotonics (%)	21	04	X 2 = 13.2, d.f = 1, p = <0.001
Number of cases where PPH occurred (blood loss >500 ml)	7	3	X 2 = 1.68, p = 0.19
Mean difference in the hemoglobin before and after delivery in g/dl	0.57	0.4	t = 3.90,3.33, p = 0.99
Number of cases who required blood transfusion	2	0	X 2 = 2.02, p = 0.15
Maternal mortality	0.8	0	–

There was a reduction in postpartum hemoglobin (Hb) in both the groups. The mean difference in group A was 0.57 mg/dl and in group B was 0.4 mg/dl. The difference in reduction in Hb between two groups was not statistically significant ($p = 0.99$). Blood transfusion was required in 2 patients for blood loss >500 ml in oxytocin group; none was required in carboprost group. There was no maternal mortality in either group due to PPH.

Both groups had similar incidence of nausea, vomiting, shivering and febrile episodes (Table 4). There were significantly more women who had diarrhea in the carboprost group [1 vs 8 %; RR = 8 (1.01–62.7), p = 0.04]. Diarrhea was observed more in patients who received therapeutic dose of carboprost (250 µg) for excessive bleeding.

Table 4 : Side effects Values indicate the percentage

	Group A (oxytocin)	Group B (carboprost)	Relative risk (95 % CI)
Nausea	2	2	RR = 1 (0.14–6.98), p = 1.00
Vomiting	0	2	RR = 5 (0.24–102.8), p = 0.29
Shivering	2	4	RR = 2 (0.3–10.6), p = 0.4
Diarrhea	1	8	RR = 8 (1.01–62.7), p = 0.04
Temperature >37.5 °C	1	2	RR = 2 (0.18–21.7), p = 0.5

DISCUSSION

The results of our study demonstrated that intramuscular carboprost tromethamine 125 µg was more effective in reducing the duration of third stage of labor, blood loss, the need for additional uterotonics than oxytocin 10 units administered intramuscularly. The side effects observed in both the groups were similar except for diarrhea, which was more common in patients who received carboprost. Diarrhea was observed more in patients who received therapeutic dose of carboprost (250 µg) for excessive bleeding.

Postpartum hemorrhage is one of the most important causes for maternal deaths worldwide, with uterine atony seen in 70–90 % of the cases. The primary aim in the management of PPH should be its prevention. Active management of the third stage with routine prophylactic administration of oxytocics at the time of delivery of the anterior shoulder of the fetus has been shown to reduce the risk of postpartum hemorrhage by about 40 % [5, 10].

Studies show that there are still wide variations in practice around the world in the management of third stage of labor. Various drugs and

routes of administration have been tested with varying success. While it is clear that use of prophylactic uterotonics will substantially reduce the bleeding in the third stage of labor and prevents PPH, the most cost-effective and ideal uterotonic has not been elucidated [6, 11].

Oxytocin is the most commonly used uterotonic and has been well known in midwifery for a long time [12]. Studies have shown that the routine prophylactic use of oxytocin may reduce the need for additional uterotonics [12, 13]. However, this was not the case in our study where additional uterotonics were required in 21 % who received oxytocin compared to only 4 % who received carboprost which is statistically significant ($p < 0.01$). The need for additional uterotonic along with the primary drug indicates the risk of postpartum hemorrhage in spite of administration of the primary drug for its prevention. Though commonly used, oxytocin is not a potent drug and often additional drugs are required and blood loss is more compared with other drugs [5]. The use of oxytocin is limited by its dose in cases of excessive bleeding due to saturation of the myometrial receptors; further increase in dose will lead to coronary artery contraction, hypotension and water retention. Methyl ergometrine is another potent uterotonic agent which was used extensively earlier. But it fell into disrepute because of its unpleasant side effects like hypertension and its contraindication in certain cases [11].

Carboprost tromethamine (PGF2α) is a powerful uterotonic agent with a physiological role in human parturition both in the delivery of the fetus and control of postpartum bleeding. The discovery of prostaglandins and their analogues as uterotonics has improved the management of PPH due to their significant influence on uterine tone, which results in minimizing the blood loss; this outweighs its cost. The side effects are also subtle [14, 15].

Few studies have examined the usefulness of prophylactic dose of carboprost in the prevention of PPH with promising results. Vaid et al. [16] compared prophylactic sublingual misoprostol, intramuscular methyl ergometrine and intramuscular carboprost for the active management of the third stage of labor and found that all these drugs were equally effective in the prevention of PPH, although diarrhea was the common complaint with carboprost.

Abdel-Aleem et al. [17] compared carboprost and methyl ergometrine in 150 women and observed that the duration of third stage of labor and mean blood loss were significantly less with carboprost.

Our study has demonstrated that carboprost is a potent uterotonic and effectively prevented PPH in 97 %, and only four patients required additional uterotonic compared to oxytocin where 21 patients received additional drugs to prevent excessive bleeding. Jing Bai et al. [18] compared oxytocin and carboprost for the prevention of PPH in high-risk patients undergoing cesarean delivery and observed that carboprost was more effective than oxytocin in preventing PPH. Vomiting was relatively common in those who received carboprost in their study.

The present study showed a reduction in the mean duration of third stage of labor (6.05 vs. 7.02 min) in patients who received carboprost which is statistically significant ($t = 3.12$, $p = 0.002$) compared to patients who received oxytocin. There are no studies which compared the mean duration of third stage of labor between oxytocin 10 units and carboprost 125 μg in the prophylaxis of PPH.

In the present study, the mean blood loss in third stage was 150 ml in the carboprost group and 251 ml in the oxytocin group which was statistically significant ($p < 0.01$). Only 3 cases developed PPH in carboprost group, whereas seven women had PPH in oxytocin group and were managed by the usual institutional PPH protocol. Various studies have shown that the mean blood loss with carboprost 125 μg was less compared to methyl ergometrine. Few studies have compared carboprost with syntometrine, which did not show any difference in mean blood loss in both the groups [4]. In the study by Jing Bai et al. [18], the median blood loss in the carboprost group was significantly lower than oxytocin and oxytocin plus carboprost groups (438 vs. 610 vs. 520 ml, both $p < 0.05$) in high-risk patients undergoing cesarean delivery.

Hemoglobin was slightly reduced in both the groups postdelivery. The mean difference in hemoglobin was less in oxytocin group, which was not statistically significant. Two women required blood transfusion in oxytocin group for excessive bleeding and none in carboprost group. Carboprost in therapeutic dose (250 μg) has been reported to be effective in 84–96 % in the treatment of PPH and may avoid the need for surgical interventions [19]. However, the therapeutic dose of carboprost invariably induces vomiting, diarrhea, rise in temperature and asthma in patients.

Patients may also experience hot flushes, sweating and irritability. But these side effects are much less with prophylactic dose, 125 μg. In our study, diarrhea was significantly more common in carboprost group than oxytocin ($RR = 8$, $p = 0.04$). All other side effects were comparable to oxytocin group.

CONCLUSION

In conclusion, our study emphasizes that carboprost 125 μg is a better, cost- effective alternative compared to intramuscular oxytocin 10 units and more effective in active management of third stage of labor. may be considered in all patients including hypertensives where methyl ergometrine is contraindicated and also in women at risk of PPH. However, a large multicentric randomized controlled trial is required to draw a conclusion.

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