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CARBOPROST: A PROMISING PREVENTIVE APPROACH FOR THE POSTPARTUM HAEMORRHAGE

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Keywords:

AMTSL - Active management of third stage of labour, Carboprost, Uterine atony, PPH – Post Partum Hemorrhage

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ABSTRACT: Background: Childbirth is a multi-stage process, and the postpartum period holds significant implications for maternal health. The third stage of labour, when the placenta detaches, is the most dangerous for women because of excessive bleeding (postpartum hemorrhage or PPH). This is often caused by the uterus not contracting properly (uterine atony). Thus, there's a well-established practice called active management of the third stage that helps to prevent these complications. **Objectives:** To assess the efficacy and safety of carboprost in active management of third stage of labour. **Methodology:** Sixty parturient were enrolled in a study. Following the delivery of the baby's anterior shoulder, these parturient received a single intramuscular injection of 125 microgram of carboprost. The primary outcomes assessed were the duration of the third stage of labour, the amount of blood loss, and the incidence of postpartum hemorrhage (PPH) **Results:** This study group experienced an average third stage of labor duration of 5.25 ± 1.73 minutes, accompanied by an average blood loss of 157.41 ± 49.43 ml and the need for additional uterotonics was minimal. **Conclusion:** Our study concludes that Carboprost, adose of 125 microgram exhibits a promising uterotonic profile, indicating its potential suitability as a prophylactic medication within active management protocols for the third stage of labour. Further investigation is necessary to confirm this potential benefit.

INTRODUCTION: Postpartum hemorrhage (PPH), characterized by excessive blood loss following childbirth, remains a significant global threat to maternal health. In India, Cesarean sections (C-sections) have a higher risk of postpartum hemorrhage (PPH) at 6% compared to the 2-4% rate observed in vaginal deliveries. PPH is a major contributor to maternal mortality in India, claiming roughly one-quarter of mothers' lives [1]. Postpartum hemorrhage (PPH) is a significant obstetric complication defined as blood loss exceeding 500 ml following vaginal birth or 1000 ml after cesarean delivery within the first 24 hours. This severe condition, often caused by uterine atony, is classified into minor (500-1000 ml) and major (more than 1000 ml) categories, with the latter further subdivided into moderate (1001-2000 ml) and severe (more than 2000 ml) blood loss [2].

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Uterine atony, characterized by a weak and flaccid uterus following childbirth, stands as the primary cause of postpartum hemorrhage (PPH). Contributing factors include genital tract trauma, uterine rupture, retained placental tissue, and maternal coagulation disorders [3]. In the latter part of the twentieth century, a novel approach called 'active management of the third stage of labour' emerged. This method aims to prevent postpartum hemorrhage by administering a uterotonic immediately after delivering the baby's anterior shoulder. It involves clamping and cutting the cord,

along with controlled cord traction to facilitate placental expulsion [4]. Uterotonic therapy has shown to reduce the incidence of PPH by 40% [5]. Healthcare providers often rely on pharmacological treatment when addressing postpartum hemorrhage (PPH). Several different uterotonic drugs have been used for preventing PPH which includesoxytocin, ergometrine, misoprostol, carbetocin, and their combinations [6].

Novel drug carboprost tromethamine, a synthetic version of the natural hormone prostaglandin F2α, works by preventing the breakdown of another molecule (15-hydroxydehydrogenase). This, in turn, strengthens contractions in the uterus (enhancing uterine tone), and effectively reduces the blood loss during the critical postpartum period [7]. Furthermore, carboprost with its extended half-life compared to traditional prostaglandins translates to a high success rate (84-96%) in treating and preventing postpartum hemorrhage by promoting sustained uterine contractions, often obviating the need for surgery [8]. Therefore, to investigate this promising potential, this study evaluates the efficacy and safety of carboprost tromethamine in preventing postpartum hemorrhage during the third stage of labour.

MATERIALS: This prospective, open-label study, conducted over an eighteen-months period, evaluated the efficacy of carboprost tromethamine in preventing postpartum hemorrhage in a sample of sixty parturient with singleton pregnancies. The sample size was determined to achieve 80% power at a 95% confidence level. The study recruited parturients with singleton pregnancies at 37-42 weeks gestation, anticipating vaginal delivery in vertex presentation, and who provided written informed consent. Exclusion criteria included patients declining participation, those scheduled for cesarean section, and those with singleton pregnancies the gestational range of <37 and >42 weeks, known hypersensitivity to oxytocin, misoprostol, or carboprost, or presenting with contraindicated medical/obstetric conditions.

METHODOLOGY: Following ethical approval (No.BMC/PGs/289), this prospective study recruited parturient at the labour wards of Vani Vilas Hospital who met the inclusion criteria: singleton pregnancy (37-42 weeks), anticipated vaginal delivery with vertex presentation, and willingness to provide written informed consent. Sociodemographic data and comprehensive clinical history (general, systemic, and obstetric) were collected using a standardized case record form. Following the delivery of the baby's anterior shoulder, the study parturient received an intramuscular dose of 125-microgram carboprost tromethamine as outlined in the study protocol.

The efficacy and safety of carboprost tromethamine were evaluated using a set of primary and secondary outcomes. The primary outcomes assessed were the duration of the third stage of labour (time from baby delivery to placental expulsion) andthe amount of blood loss (measured using soaked materials after replacing standard drapes with calibrated ones, providing a more accurate estimation).Secondary outcomes assessed were the need for additional uterotonics, blood transfusions, complications such as hysterectomy and ICU admissions, and changes in hemoglobin/hematocrit levels 24 hours postpartum. Safety was ensured by monitoring for adverse reactions using the WHO causality scale.

RESULTS: Carboprost demonstrated promising efficacy in preventing postpartum haemorrhage (PPH). In a population predominantly consisting of young, primiparous women with full-term pregnancies (n=60), carboprost effectively reduced blood loss and the duration of the third stage of labour. A significant majority (93%) of participants experienced minimal blood loss (<250 ml), with an average of 157.41 ± 49.43 ml. This represents a substantial reduction in blood loss compared to historical rates. Carboprost effectively shortened the duration of the third stage of labor to an average of 5.25 ± 1.73 minutes, demonstrating its potential to improve maternal outcomes. Mild side effects were observed in a small percentage of participants (e.g., fever, diarrhea, nausea, vomiting). However, these effects were generally manageable and did not significantly outweigh the benefits of carboprost in preventing PPH.

DISCUSSION: Postpartum haemorrhage (PPH) poses a significant challenge for clinicians, a substantial number of maternal deaths related to PPH are preventable. Early diagnosis and prompt treatment are crucial in modifying this

complication. Active management of third stage of labour (AMTSL) has emerged as a key strategy for reducing PPH incidence. This approach involves the administration of uterotonic medications, either following caesarean section or during the third stage of labour for vaginal delivery. Studies have demonstrated that AMTSL can be an effective preventive measure against PPH [10, 11, 12].

Despite recent research, significant variations persist globally in managing the third stage of labour. While Methyl ergometrine remains widely used, its association with unpleasant side effects like hypertension raises concerns about its suitability. Intramuscular oxytocin, endorsed by the World Health Organization, offers a more favorable side-effect profile compared to Methyl ergometrine [12, 13]. Oxytocin, though its efficacy is often augmented by additional uterotonic agents, it remains a corner stone in the treatment of PPH [13]. Prostaglandin F2α (PGF2 α) emerges as a powerful natural substance with its vital role in delivering the baby and also helps in controlling bleeding after birth (postpartum hemorrhage). The discovery of PGF2α and similar analogues like carboprost, which have a strong, long-lasting effect on uterine contraction, particularly in the lower segment, and require only small doses, has significantly transformed modern medicine's approach to the prevention of postpartum hemorrhage [14, 15]

Sociodemographic and Obstetric Characteristics: As shown in the table 1, nearly three-fourth (75%) of our study population were in the age group of 20-25 years of the young women with singleton pregnancies, which aligns with findings reported by Singh *et al.* [14]. Primiparous women, accounting for 63% of our study population, were at a higher risk of postpartum hemorrhage compared to multiparous women, consistent with previous research, and this increased risk is often attributed to factors such as uterine inexperience and the greater likelihood of uterine atony following delivery [15].

In addition to the above findings, our study revealed that the majority of parturients (53.3%) progressed to full term (38-39 weeks), highlighting the importance of gestational age for optimal neonatal outcomes. Newborns delivered before or after the optimal gestational range of 38-39 weeks may face increased risks of complications [16].

TABLE 1: DEMOGRAPHIC AND OBSTETRIC CHARACTERISTICS OF STUDY POPULATION

Demographic and Obstetric characteristics		Carboprost (n=60)
Age group (years)	≤20	24(40%)
	21-25	23(38.3%)
	26–30	11(18.3%)
	>30	02(3.3%)
	Meanage±SD	22.53±3.71
Parity	Primi	38 (63%)
	Multi	22 (37%)
Period of Gestation (in weeks)	37-38	17 (28.3%)
	38-39	32 (53.3%)
	39-40	11 (18.3%)

Characteristics of Obstetric Intervention: The most common method of natural childbirth occurs primarily through spontaneous delivery, which aligns with our study (70%), and the remaining 30% requiring induction.

Episiotomy was performed in a significant proportion (88.3%) of deliveries in our study, reflecting its widespread use in the general population. However, the need for additional uterotonics was minimal (3%), indicating that the initial administration of carboprost was generally effective in preventing postpartum hemorrhage.

TABLE 2: CHARACTERISTICS OF OBSTETRIC INTERVENTION

Characteristics of obstetric Intervention		Carboprost (n=60)
Mode of delivery	Induced	18 (30%)
	Spontaneous	42 (70%)
Requirement of Episiotomy	Required	53 (88.3%)
	Not required	7 (11.7%)
Additional uterotonic	Required	2(3%)
	Not Required	58(93%)

In the present study mean duration of third stage of labour was 5.25±1.73 minutes, which is in accordance with the study done by Lamba A and

Chua S *et al.*[5] The results of our study did not match with the findings of the following studies done by Reddy *et al.*, [17] Bhattacharya *et al.*, [18] and Anjaneyulu *et al* [19]. Carboprost tromethamine, a potent uterotonic agent, with a physiological role in human parturition exerts its effects primarily by stimulating myometrial contractions which can lead to a reduction in the duration of labour. The novel drug carboprost significantly shortened the third stage of labour to 2.63 minutes in the study done by Purushottam *et al* [20]. (2008), highlighting its potential benefits for maternal health. Carboprost, by binding to the prostaglandin E2 receptor, results in increased uterine tone and contractions that facilitate the expulsion of the placenta and this suggests its potential benefits in preventing postpartum hemorrhage [21, 22].

TABLE 3: DISTRIBUTION OF PATIENTS ACCORDING TO DURATION OF THIRD STAGE OF LABOUR

Duration (min)	Participants (%)
2 – 4 minutes	15
4– 6 minutes	32
6 – 8 minutes	11
8-10 minutes	1
>10 minutes	1

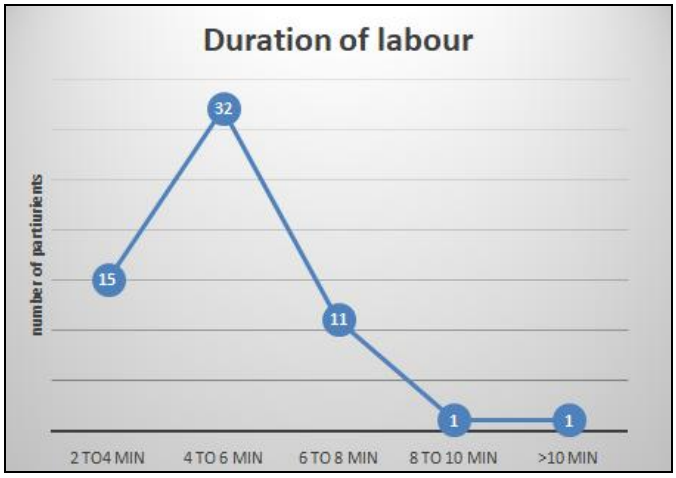

FIG. 1: DISTRIBUTION OF PATIENTS ACCORDING TO DURATION OF THIRD STAGE OF LABOR

Carboprost proved exceptional efficacy in preventing severe postpartum hemorrhage, with 93% of participants experiencing minimal blood loss (< 250 ml) and the mean blood loss in the third stage of labour was 157.41 ± 49.43 ml as shown in the table-4 of our study, and which is comparable to the findings reported by Reddy *et al.*[17] Visual estimation of blood loss can significantly underestimate the severity of postpartum hemorrhage (PPH), potentially leading to undertreatment. Accurate assessment of blood loss requires laboratory tests such as hemoglobin, hematocrit, and red blood cell count. A decrease in these values indicates blood loss, highlighting the escalating risk of PPH as blood loss increases.

TABLE 4: DISTRIBUTION OF PATIENTS ACCORDING TO AMOUNT OF BLOOD LOSS DURING THIRD STAGE OF LABOUR

Amount of Blood loss (ml)	Participants (%)
<=100 ml	9
101-150 ml	20
151-200ml	21
201-250 ml	5
251-300 ml	4
301-350 ml	1
351-400 ml	0
401-450 ml	0
451-500 ml	0
>500 ml	0

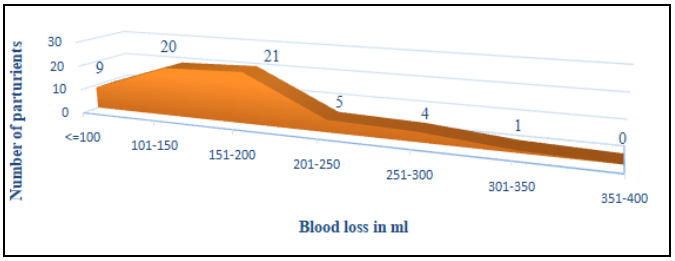

FIG. 2: DISTRIBUTION OF PATIENTS ACCORDING TO AMOUNT OF BLOOD LOSS - THIRD STAGE OF LABOUR

Mean change in Hb and HCT: After childbirth (puerperium), hemoglobin levels naturally dip in the first few days, as fluids move from tissues into the bloodstream, replacing blood lost during delivery [23]. Hemoglobin levels can drop significantly within the first four days after delivery, reaching a decrease of up to 3.5 grams per deciliter [24]. Consistent with previous research by Sneha *et al.*, as seen in the **Table 5** of our study, observed a significant decline in hemoglobin (Hb) levels following childbirth. The average pre-partum Hb concentration decreased from 11.2±1.3 g/dL to 10.7±1.3 g/dL within the first postpartum day. Similarly, hematocrit levels experienced a statistically significant decline during this period [25]. Thus, the statistically significant decline in hemoglobin (Hb) and hematocrit (Hct) levels observed during the postpartum period is likely attributed to a combination of physiological changes, including blood volume dynamics, suppression of erythropoiesis, and potential

hemolysis. Monitoring these levels is crucial for timely intervention and management of postpartum anemia. As shown in the results of the present study, Carboprost was associated with mild adverse effects, primarily fever, diarrhea, nausea, and vomiting. However, these side effects were infrequent, occurring in a small percentage of participants. While these adverse effects are relatively mild and manageable, it's important to note that individual responses to carboprost may vary. Healthcare providers should be aware of these potential side effects and monitor patients accordingly.

TABLE 5: PRE- AND POST-DELIVERY HEMOGLOBIN AND HAEMATOCRIT LEVELS

Participants	Pre-Partum	Post-Partum	Dropin	P value	95% Confidence interval	
					Lower	Upper
Mean Hb	11.2±1.3	10.7±1.3	0.6±0.1	<0.0001*	10.89	11.56
Mean HCT	33.9±3	32.3±3.5	1.6±1	<0.0001*	33.15	34.74

HCT -hematocrit - one sample T test, *P value <0.05 -statistically significant.

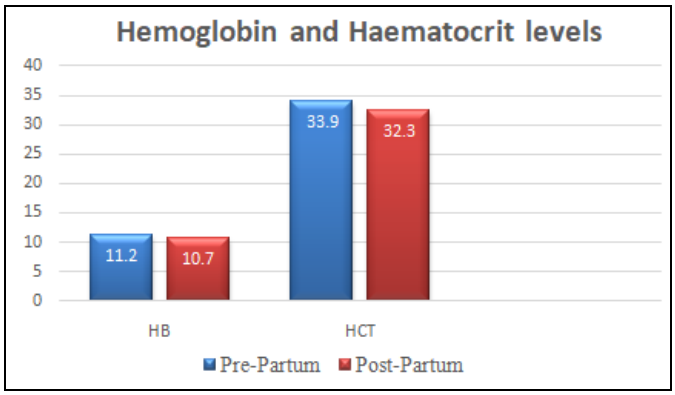

FIG. 3: PRE-AND POST-DELIVERY HEMOGLOBIN AND HEMATOCRIT LEVELS

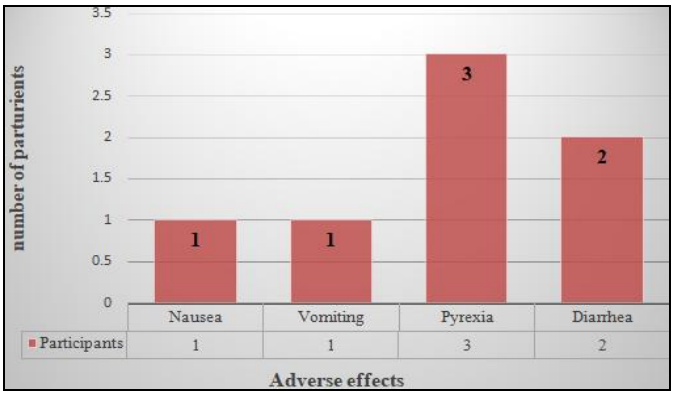

FIG. 4: ADVERSE EFFECTS

Strengths and Limitations: The study aligns with current recommendations for active management of the third stage of labour, employing objective blood loss measurement with Brass V drapes and assessing hematocrit concentration. The findings demonstrate promising results, with carboprost leading to minimal blood loss in most participants and a low need for additional uterotonics. The lack of blinding could have introduced bias and being the single-centre design limits generalizability of the results. These limitations highlight the need for further research with a larger, multicentre design and a blinded approach to definitively establish the effectiveness of carboprost for PPH prevention.

CONCLUSION: Based on the findings of this study, carboprost emerges as a promising preventive measure for postpartum haemorrhage (PPH). The significant reduction in blood loss observed, coupled with the low incidence of severe adverse effects, highlights the drug's efficacy and safety profile. Overall, this study provides compelling evidence for the integration of carboprost into clinical practice as a valuable tool in reducing the risk of postpartum hemorrhage and improving maternal outcomes.

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CONFLICT OF INTEREST: None declared

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