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Carboprost versus oxytocin for active management of third stage of labour

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Abstract: *Background and Objectives:* Postpartum haemorrhage is a single largest and leading cause of maternal morbidity and mortality not only in developing countries but also in developed countries. Every 4 minutes one women die from pregnancy or child birth related complications. The present study is an attempt to evaluate the scope of using prophylactic intramuscular carboprost tromethamine 125µg in comparision with intramuscular oxytocin 10U for the active management of third stage of labour. *Materials and Methods:* Two hundred pregnant women at term with spontaneous onset of labour were included in the study and were randomly divided into 2 groups of 100 women each. Group A and Group B were given Inj.Oxytocin 10 units and Inj. carboprost tromethamine 125 ug intramuscular respectively at the time of delivery of anterior shoulder. The main outcome measures with respect to third stage of labour were: duration, blood loss by volume, difference in hemoglobin, need for additional oxytocics and side effects. *Results:* Carboprost tromethamine group had a significant reduction in duration of third stage ($p < 0.05$) and blood loss ($p < 0.0001$) when compared to oxytocin group. *Conclusion:* Intramuscular carboprost is better alternative to intramuscular oxytocin in active management of third stage of labour.

Keywords: Active Management of Third Stage of Labour, Carboprost, Oxytocin.

Introduction

The third stage of labour is the most crucial stage, 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 is one of the dreaded complication of third stage of labour. In India every 4 minutes a woman dies during child birth [2]. Maternal mortality rate in India is 212 per 100000 live births. Among them 30% of deaths are due to postpartum hemorrhage (PPH) [3].

Reducing likelihood of postpartum hemorrhage by routine active management of third stage of labour could play an important role in reducing maternal mortality and morbidity in modern obstetrics. The decrease in the problems associated with third stage of labour 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 includes oxytocin, methylergometrine and 15 methyl PGF2α (Carboprost) [6]. Recent studies have shown that there are still wide variations in practice around the world in the management of third stage of labour [7-8]. Prophylactic use of oxytocic agents 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 postpartum eclampsia, intracerebral haemorrhage, myocardial infarction, cardiac arrest and pulmonary oedema [2]. Carboprost tromethamine is a PGF2 α analogue. It is given as a single intramuscular injection. It is free from side effects such as hypertension [9].

The present study is an attempt to evaluate the scope of using carboprost tromethamine in comparison with intramuscular oxytocin, which is being used by many clinicians in our country for the active managements of third stage. Pharmacokinetics of carboprost tromethamine has limited number of studies and its efficacy in controlling PPH is not properly studied.

This study attempts to evaluate use of carboprost in comparision to oxytocin in active management of third stage of labour.

Aims and Objectives:

1. To compare the effectiveness of intramuscular oxytocin 10units and intramuscular carboprost tromethamine (125µg) in prophylaxis of post partum haemorrhage.
2. To compare the amount of blood loss in third stage.
3. To compare the duration of third stage.
4. To evaluate the side effects

Material and Methods

This prospective study was conducted at Al Ameen medical college during the period of one year from November 2014 to October 2015. This study was performed on 200 cases with 100 cases in each group. Patients assigned to group 1 received 10 units oxytocin intramuscularly and group 2 received carboprost 125µg intramuscularly at the time of delivery of anterior shoulder of baby.

Inclusion Criteria: Primigravida or multigravida with singleton pregnancy with cephalic presentation with no obstetric complications in whom vaginal delivery is anticipated.

Exclusion criteria: Patients with hypersensitivity to drugs, respiratory diseases, cardiac disease, renal, liver disorder, epilepsy, psychiatry disorder, Preeclampsia, Severe anemia, Multiple pregnancy Poly/Oligohydramnios, Past History of PPH, Grand Multipara.

An Informed written consent was obtained from each patient who fulfilled inclusion & exclusion criteria. Selected patients were evaluated by history, physical examination, systemic examination & internal examination. Routine investigations were sent. Ethical clearance was taken from the hospital.

Statistical Analysis: The amount of blood loss, length of the third stage, third stage complications, sideeffects like nausea, vomiting, diarrhoea, shivering, retained placenta and need for second injection of additional oxytocics were noted. Hemoglobin (Hb) in gm% was estimated at the time of admission and 24hours after delivery. The blood loss during third stage of labour and the immediate postpartum period (1 hour after delivery) was estimated quantitatively using *Brasss V Drape.*

Data was entered in to Microsoft Excel® and analysed 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 was normally distribute in all the groups. Data were summarized as mean & proportion. Unpaired t test was used to test the difference in between two different groups. Paired data was anlysed using paired t test. Chi square test was used to analyse the difference in proportions

Results

This study was performed on 200 cases with 100 cases in each group. Patients assigned to group 1 received 10 units oxytocin intramuscularly and group 2 received carboprost 125µg intramuscularly at the time of delivery of anterior shoulder of baby. Descriptive statistical tools like mean and proportion are used to calculate the data. Student t test and chi suare test are used to compare the efficacy of two drugs.

Table-1: Distribution of study subjects according to duration of III stage of labour

Duration (Mins)	Oxytocin	Carboprost	Total
2 – 4	15 (15)	20 (20)	37
4 – 6	20 (20)	35 (35)	55
6 – 8	40 (40)	25 (25)	65
8 – 10	20 (20)	16 (16)	36
>10	5 (5)	4 (4)	9
Total	100 (100)	100 (100)	200

Numbers in the parenthesis indicate column percentage ($X^2 = 8.82$, d.f = 4, p = 0.09). The maximum number of women (40%) in group 1 (Oxytocin) had duration of third stage of labour ranging between 6 to 8 minutes and in group 2 (Carboprost), the maximum number of women had duration of third stage ranged between 4-6 minutes. There was no staisticlly significant difference between the two groups. (p= 0.09).

Table-2: Comparison of mean duration of III stage labour between two groups				
Duration of Third stage of labour (Minutes)	Oxytocin (Mean ± SD)	Carboprost (Mean ± SD)	Mean difference	Statistical analysis
	7.02 ± 2.6	6.05 ± 1.7	0.97	t = 3.12 p= 0.002 (Significant)

The mean duration of third stage of labour in group 1(oxytocin, 7.02 ± 2.6 mis) was statisitcally significantly higher than in group 2 (carboprost, 6.05 ± 1.7 mins). (t = 3.12, p=0.002).

Table-3: Distribution of study subjects according to amount of blood loss			
Blood loss (ml)	Oxytocin n (%)	Carboprost n (%)	Total
<100	02 (2)	15 (15)	17 (8.5)
101-150	03 (3)	30 (30)	33 (16.5)
151-200	10 (10)	32 (32)	42 (21)
201-250	29 (29)	13 (13)	42 (21)
251-300	35 (35)	06 (6)	41 (20.50)
301-350	15 (15)	03 (3)	18 (9)
351-499	04 (04)	01 (1)	5 (2.5)
>500	02 (02)	00 (0)	2 (1)
Total	100 (100)	100 (100)	200 (100)

The above table shows that majority of study subjects (~85%) in group 1 (Oxytocin) has blood loss more than 200 ml, and the majority of subjects (~75%) in group 2 (Caboprost) had blood loss than 200 ml. The difference was statisitically significant (p<0.001).

Table-4: Comparison of mean amoount of blood loss (ml) in two groups				
Blood loss (Milliliters)	Oxytocin (Mean ± SD)	Carboprost (Mean ± SD)	Mean difference	Statistical analysis
	281.05 ± 84.83	170.2 ± 50.2	110.85	t = 11.24, p <0.0001 (Significant)

The blood loss in group 1 (oxytocin, 281.05± 84.83 ml) was statistically significantly more compared to group 2 (carboprost, 170.2 ±50.2.ml). (t = 11.24, p< 0.0001).

Table-5: Comparison of additional oxytocics requirement in two groups			
Additional Oxytocics	Oxytocin	carboprost	Total
Required	21 (21)	04 (4)	25 (12.5)
Not required	79 (79)	96 (96)	175 (87.5)
Total	100 (100)	100 (100)	200 (100)

Numbers in the parenthesis indicate column percentage (X^2 = 13.2, d.f = 1, p <0.001). Number of patients requiring additional uterotonics in oxytocin group are more (21%) compared to carboprost group (4). Additional oxytocics in the form of methylergometrine 0.2mg, misoprostol (PGE1) was provided.The difference was statistically significant

Table-6: Comparision of hemoglobin changes in two groups				
	Before delivery	After delivery	Mean difference (Reduction in Hb)	Paired t test
Oxytocin (Mean ± SD)	9.68 ± 1.39	9.11 ± 1.46	0.57	t = 3.90 p = 0.99
Carboprost (Mean ± SD)	9.75 ± 1.2	9.35 ± 1.2	0.4	t = 3.33 P=0.99

There was reduction of postpartum hemoglobin in both the groups.mean difference in group A was 0.57 and in group B was 0.4. The difference in reduction in Hb between twoe groups was not statistically significant (p = 0.99).

Table-7: Comparision of side effects		
Side effects	**Oxytocin**	**Carboprost**
Nausea	04	05
Vomiting	02	04
Shivering	02	00
Diarrhea	00	08
Headache	02	00

Women in group A had side effects like nausea, vomitting and other side effects like shivering, headache. Women in group B had common side effect diarrhea of about 3%, nausea (1.5%) and vomiting (1.5%)

Discussion

Postpartum hemorrhage is one of the most important cause for maternal deaths throughout the world. Active management of third stage of labor and the use of prophylactic oxytocics has reduced its incidence in many countries. The primary aim in the management of postpartum hemorrhage should be its prevention. The 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].

Recent studies show that there are still wide variations in practice around the world in the management of third stage of labour. Methyl ergometrine is a conventional oxytocic used extensively but is associated with unpleasant side effects like hypertension. Intramuscular oxytocin used alone has been found effective in preventing postpartum hemorrhage with fewer side effects and is recommended by world health organization but most of the times additional uterotonics are required [8,11]. Various drugs and routes of administration have been tested with varying success. Oxytocin is probably the most commonly used oxytocic and has been well known in midwifery for a long time. Though commonly used it is not the potent drug and many a times requires additional drugs and blood loss is more compared with other drugs [11].

The production of PGF2α in the decidual tissue was found to be more when obtained during labour indicating the increase in the synthesis and release of PGF2α into the circulation. PGF2α is a powerful uterotonic agent with a physiological role in human parturition both in the delivery of the foetus and control of post partum bleeding. The discovery of prostaglandins and its analogues as an oxytocics has improved prospect in modern era in control of PPH due to its significant influence on uterine tone resulting in minimizing blood loss which outweighs its cost. The side effects are also subtle [12-13]. Hence this study was conducted at Al Ameen medical college to evaluate the two uterotonic drugs. This study has shown that carboprost tromethamine was more potent than Oxytocin in managing the third stage of labour.

In the present study, the mean maternal age (years) in oxytocin group was 22.78 ± 2.82 and carboprost tromethamine group is 22.50 ± 2.8. The Z value is 0.067 and $p > 0.05$, the difference in age groups is not significant. The age group ranged between 18-30 years and majority of the women in both the groups belonged age group of 21-25 years. The distribution of parity shows that majority of the women in both the groups were almost similar.

Table-8: Mean duration of third stage			
Study	**Methyl ergometrine**	**Carboprost**	**Oxytocin**
Singh nisha et al [20]	5.52 minutes	6.10 minutes	-
Anjaneyu et al [13]	6.1 minutes	3.5 minutes	--
Bhattacharya et al [4]	8.08 minutes	4.8 minutes	-
B.jajupuroshotam et al [19]	3.6 minutes	2.63 minutes	-
Present study	-	6.05 minutes	7.02 minutes

There are no studies comparing oxytocin and craboprost125μg for prophylaxis in low risk women. There are few studies where carboprost has been compared with methyl ergometrine and found that the mean duration of third of labour with carboprost was comparable to our study [14-15]. As

compared to other studies and in accordance with it, the present study showed decrease in mean duration of carboprost was 6.05 minutes compared to oxytocin 7.02 minutes. Therefore carboprost can be effective in reducing the duration of third stage of labour.

Table-9: Comparision of estimated blood loss in ml

Study	Methyl ergometrine	Carboprost	Oxytocin
Reddy et al [14]	202 ml	127ml	-
B.jajupuroshotam [19]	169ml	111ml	-
Present study	-	170ml	281ml

Various studies have shown that the mean blood loss with carboprost 125µg was less compared to methyl ergometrine. Few studies compared carboprost with syntometrine, which did not show any difference in mean blood loss in both the groups [14]. In the present study mean blood loss in third stage in carboprost was 170ml and oxytocin was 281 ml. (p value of 0.0001) which was highly significant [11]. None of them developed PPH in carboprost group but 10 women had PPH in oxytocin group. This was comparable with other studies as shown in the table.

Hence carboprost is effective in reducing blood loss and carboprost has sustained impact on tone of uterus. Hemoglobin was slightly reduced in both the groups but was not statistically significant. Only mean difference was less in oxytocin group. Two required blood transfusion in oxytocin group and none in carboprost group. The need for additional oxytocics along with the primary drug indicates the risk of postpartum hemorrhage inspite of administration of the primary drug for its prevention. In the present study, carboprost group required less additional oxytocics in carboprost (4%) compared to oxytocin(21%) which was statistically significant.

Side effects were more in carboprost group compared to oxytocin group. When carboprost is given in dosage of 250µg it is associated with more side effects like diarrhea, nausea, vomiting compared with 125µg. Less dosage is well tolerated with subtle side effects [15-16]. Oxytocin almost had no or minimal sideeffects whereas in carboprost group diarrhea was seen in 8% of patients and other common side effects seen were nausea and vomiting. From the above study it was observed that carboprost is an excellent drug in active management of third stage of labour to reduce duration of third stage and blood loss. Drawback in using carboprost is its storage in cold chain at 2- 4 celsius while oxytocin can be stored at room temperature.

The developing countries are benefited by the availability of strong uterotonic drug carboprost because it reduces blood loss which is important because two third of the pregnant women are anemic in these countries [17-18].

Conclusion

Carboprost when used prophylactically results in minimal blood loss with fewer side effects. This small dose 125µg is well tolerated by the patients. An added advantage is it can be used in patients with hypertension and cardiovascular disease. In India where anemia highly prevalent,the risk of PPH is very high. Intramuscular carboprost, a potent uterotonic is a desirable drug as it is well tolerated in small doses and significantly reduces the risk of PPH by limiting duration of 3rd stage of labour & by reducing the blood loss.

Our study emphasizes that carboprost is better alternative to intramuscular oxytocin in active management of third stage of labour.

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Oxytocin: prophylaxis for the third stage of labour and PPH management. > Regularly observe for response to the oxytocin infusion > Once response is achieved: > Observe for vaginal blood loss, fundal tone, blood pressure and pulse half hourly for four hours or as clinically indicated.Â oxytocin for the third stage of labour. Cochrane Database of Systematic Reviews 2004, Issue 1. Art. No.: CD000201. DOI: 10.1002/14651858.CD000201.pub2.Â Double-blind comparison of carbetocin versus oxytocin in prevention of uterine atony after cesarean section. Am J Obstet Gynecol 1999;180:670-6. 12. Borruto F, Treisser A, Comparetto C. Utilization of carbetocin for prevention of postpartum hemorrhage after caesarean section: a randomized clinical trial. Keywords: Active management of third stage of labor, third stage of labor, carboprost, oxytocin, post partum haemorrhage. Edition: Volume 7 Issue 10, October 2018. Pages: 1383 - 1385.Â Dr. Vishwa Tuvar, Dr. Kahan Chavda, Dr. D. A. Chavda, "Carboprost Versus Oxytocin in Active Management of Third Stage of Labour", International Journal of Science and Research (IJSR), https://www.ijsr.net/search_index_results_paperid.php?id=ART20192200, Volume 7 Issue 10, October 2018, 1383 - 1385. Active Management Of The Third Stage Of Labour: A Prospective Cohort Study Toâ€¦ oxytocin 10 U IM and methyl ergometrine 0.2 mg IV and recommended for the prevention of post partum haemorrhage. References.Â Database of Systematic Reviews 2001, Issue 4. [17]. Sunil Kumar KS, Shyam S, Batakurki P; Carboprost versus oxytocin for Active Management of third stage of labor. J Obstet. Gynaecol India. 2016 Oct;66 (Suppl 1): 229-34. [18]. Neri-Mejia M, Pedraza-Aviles AG; Active management of the third stage of labor: Three schemes of oxytocin: randomized clinical. trial. Ginecol Obstet Mex.