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ORIGINAL ARTICLE

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Methylergometrine and carboprost tromethamine prophylaxis for postpartum hemorrhage

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OBJECTIVE(S) : To compare methylergometrine (250 □g) and carboprost tromethamine i.e. 15-methyl analogue of $PGF_2\alpha$ (125 μg) as prophylaxis for postpartum hemorrhage (PPH).

METHOD(S) : A cross-sectional randomized comparative study was carried out at our tertiary care teaching hospital on 130 women in labor. They were randomly allotted to one of the two groups. Group A included 65 women who were given methylergometrine (250 □g) intravenously and Group B included 65 women who were given injection carboprost (125 □g) intramuscularly at the time of delivery of anterior shoulder. Main outcome measures were duration of third stage, incidence of PPH and side effects of the drug. Statistical analysis was done with students t test and chi square test.

RESULTS : The two groups were comparable with regard to age and parity. 78.4% of Group A and 46.1% of Group B had one or more high risk factors for PPH (P=0.001). Mean duration of third stage of labor in the two groups was comparable and there was no case of retained placenta. Placental separation occurred within 5 minutes in 87% in Group A and in 83% in Group B (p=0.456). PPH occurred in 4.6% in Group A and 6.1% in Group B (P=1.0). Among the high-risk women, PPH occurred in 7.8% in Group A and 13.3% in Group B (P=0.55). Side effects were noted in 3% in Group A and in 12.4% in Group B (P=0.04).

CONCLUSION(S) : Methylergometrine (250□g) and carboprost (125□g) are comparable in efficacy for prevention of PPH but since side effects and the cost are significantly more with carboprost, methylergometrine should be preferred for routine use, reserving carboprost for women in whom methyleyometrine is contraindicated.

Key words : uterotonics, prophylaxis for postpartum hemorrhage, active management of third stage.

Introduction

Postpartum hemorrhage (PPH) is a major cause of maternal mortality in India. A number of drugs and surgical technics are used for prevention and control of PPH. But prevention is always better than cure and this study is focused on it.

Active management of the third stage is implemented as a 'package' including early uterotonic therapy with the delivery of the anterior shoulder, early cord clamping and placental delivery by controlled cord traction following signs of placental separation [1]. Randomized comparisons of active and expectant management of third stage have shown that the former brings meaningful reductions in incidence and severity of PPH [2].

Oxytocin and methylergometrine are the commonly used uterotonics for prevention of PPH. Syntometrine (combination of ergometrine and oxytocin), could not show any advantage over the conventional drugs.

Prostaglandin is known to have a good therapeutic role in PPH. We have evaluated the role of smaller dose of carboprost trometharine (125□g), a 15-methyl analogue of $PGE_2\alpha$ in comparison with methylergometrine (250 □g) for PPH prevention as a part of active management of third stage of labor.

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Methods

A total of 130 women in labor were included in the study after obtaining informed consent. All of them had routine antenatal investigations including hemoglobin estimation, urinalysis and blood sugar screening. They were allotted to receive either 250□g methylergometrine intravenously (Group A) or 125□g carboprost trometharine intramuscularly at delivery of anterior shoulder, by placing of random allocations into sealed, identical, consecutively numbered envelopes, which were opened only during delivery. Women with hypertension, heart disease, renal or hepatic disorder, and cesarean delivery were excluded.

All women were monitored in the third stage of labor and during postpartum period. Records were kept about duration of third stage by noting the time between delivery of the baby and complete delivery of the placenta. Perineal drapes were replaced by fresh dry ones after delivery of the baby. Amount of blood loss was estimated by weighing the blood clots and the new drapes before and after use. Results were analyzed using estimated range of blood loss instead of exact amounts. Women were also monitored for side effects like nausea, vomiting, diarrhea, headache and hypertension.

Women who developed PPH were treated with uterine massage and oxytocin infusion (15U/500mL). If needed, this was followed by the respective drug in the group i.e. methylergometrine 250□g IV or carboprost 250□g IM. No woman needed a repeat injection of methylergometrine or carboprost. Postpartum hemoglobin estimation was done in women with preexisting anemia and in those who developed PPH.

Results

All women were in the age group of 18-38 years. Mean age in Group A was 26 years and in Group B 25 years. Parity ranged from 0 to 5 in group A and 0 to 6 in Group B. There were three grand multiparas (Parity 5 or more) in Group A and two grand multiparas in Group B.

Table 1 gives the risk factors for PPH. Fifty-one (78.0%) women in Group A and 30 (46.1%) in Group B had one or more high risk factors for PPH (P=0.001).

Table 2 gives the duration of third stage of labor. Mean duration was 5.52 minutes in Group A and 6.10 minutes in Group B. Eighty-seven percent in Group A and 83% in Group B had placental delivery within 5 minutes (P=0.456). There was no case of retained placenta and no extra effort was required for placental removal in any of the cases.

Nine women developed PPH; seven due to uterine atony, one due to uterine atony and cervical tear, and one due to vaginal lacerations.

Table 1. Risk factors for PPH.

Risk factors (n=65)	Group A (n=65)	Group B
Previous cesarean delivery	10	3
Previous surgical abortion or D & C	4	3
Past history of PPH	0	1
Grand multiparity	3	2
Hydramnios	0	3
Placenta previa	1	0
Multiple pregnancy	1	0
Preexisting anemia		
Mild (Hb 8-10g/dL)	12	8
Moderate (Hb 6 to 7.9g/dL)	0	1
Severe (Hb < 5.9 9/dL)	4	3
Oxytocin use during labor	36	30
Labor following failed tocolysis	0	1
High risk for PPH	51/65 (78.0%)[a]	30/65 (46.1%)[a]

[a] P= 0.001

Table 2. Duration of third stage of labor.

Duration	Group A n = 65	Group B n= 65	P value
Mean duration	5.52 minutes	6.10 minutes	
Range	2 to 15 minutes	3 to 15 minutes	
Median	5 minutes	5 minutes	
Less than 5 minutes	56 (87%)	54 (83%)	(P = 0.456)
5 to 10 minutes	7 (10%)	6 (9.3%)	(P = 1.000)
10 to 20 minutes	2 (3%)	5 (7.7%)	(P = 0.437)

Among the low risk women, incidence of PPH was 1 in 49 i.e. 2.04%. Among the high-risk women, 4/51 (7.84%) developed PPH in Group A and 4/30 (13.30%) in Group B. The difference was not statistically significant (P=0.55).

Table 3 shows the details of those who developed PPH in Group A and Table 4 of those in Group B.

Side effects were seen in 2(3%) In Group A (vomiting-1, diarrhea-1) and in 8(12.4%) in Group B (nausea-2, vomiting-3, diarrhea 3). This difference was statistically significant (P=0.04). None developed hypertension or headache.

Table 3. Details of women with PPH in Group A.

No.	Cause of PPH	Blood loss (mL)	High Risk factor	Treatment
1.	Uterine atony	500 to 1000	Twin pregnancy Mild anemia	Uterine massage 15 U oxytocin IV drip One unit blood transfusion
2.	Uterine atony	500 to 1000	Nil	Uterine massage 15 U oxytocin IV drip Methylergometrine 250 µg 10 Carboprost 250 µg IM
3.	Uterine atony	500 to 1000	Oxytocin use during labor	Uterine massage 15 U oxytocin IV drip
4.	Uterine atony and cervical tear	500 to 1000	Oxytocin use during labor	Uterine massage µg 10 15 U oxytocin Methylergometrine Repair of cervical tear
5.	Vaginal lacerations	500 to 1000	Oxytocin use during labor	Uterine massage Repair of vaginal lacerations

Table 4. Details of women with PPH in Group B.

No.	Cause of PPH	Blood loss (mL)	High risk factors	Treatment
1.	Uterine atony	1000 to 1500	Past history of PPH History of voluntary termination of pregnancy Oxytocin use in labor	Uterine massage 15 U oxytocin IV drip Methylergometrine 250µg Carboprost 250 µg IM
2.	Uterine atony	500 to 1000	Oxytocin use in labor	Uterine massage 15 U oxytocin IV drip
3.	Uterine atony and cervical tear	1000 to 1500	Failed tocolysis Mild anemia	Uterine massage 15 U oxytocin IV drip Methylergometrine 250 µg IV Carboprost 250 mg/IM Cervical tear repair

Discussion

PPH is excessive bleeding (more than 500 mL in vaginal delivery and more than 1000 mL in cesarean section) following delivery. It can be atonic when bleeding is from the implantation site, or traumatic when bleeding is due to trauma to the genital tract or both, the incidence being 5% in all deliveries [1]. It is a major cause of maternal morbidity and mortality in both industrialized and non-industrialized countries but the absolute mortality rates are significantly higher in the developing world. This emphasizes the role of better medical care, both preventive and therapeutic, in non-industrialized countries.

Active management of third stage of labor has been advocated as prophylaxis for atonic postpartum hemorrhage. This includes early oxytocic therapy (with delivery of the anterior shoulder or shortly after delivery of the baby), early cord clamping and placental delivery by controlled cord traction following signs of separation [2]. Randomized comparisons of active and expectant management of third stage have shown meaningful reductions in postpartum hemorrhage, postpartum anemia, need for blood transfusion, and therapeutic oxytocic drugs[3]. However, adverse effects of active management include side effects of the oxytocic drugs.

Methylergometrine (250 □g) given intravenously at the

delivery of anterior shoulder has been effectively used for prophylaxis of PPH due to its strong uterotonic properties. Adverse effects of methylergometrine include nausea, vomiting, headache and hypertension.

Incidence of side effects was as low as 3.0% in those receiving 250□g methyleryometrine at the delivery of the anterior shoulder. This was significantly lower (P=0.04) than the 12.4% incidence of side effects (nausea, diarrhea and vomiting) in women who received 125□g carboprost at the delivery of anterior shoulder. It must be mentioned that women with hypertation were excluded from the study. Analysis of the results shows comparable efficacy of methylergometrine and carboprost for prophylaxis of PPH in both low risk and high-risk antenatal women. Among high-risk women, incidence of atonic PPH was 7.84% in methylergometrine group and 13.30% in carboprost group. The difference is not statistically significant (P=0.55).

None of our subjects had prolonged third stage of labor or retained placenta. In methylergometrine group 87% and in Carboprost group 83% had placental delivery within 5 minutes. None of the women with PPH had blood loss in excess of 1000 mL. PPH in all subjects was controlled with uterine massage, oxytocin infusion (15 units in 500 mL) and one dose of respective uterotonic (methylergometrine 250 □g or carboprost 250 □g in the respective group).

One unit blood transfusion was needed in a patient with PPH in methylergometrine group who had preexisting nutritional anemia of moderate severity.

A multicentric trial compared the role of $PGF_2\alpha$ (125□g) and methylergometrine for PPH prophylaxis in 300 patients[4]. This trial showed significantly shorter duration of third stage and reduced amount of blood loss in carboprost group.

The most recent Cochrane Review [5] of 17 misoprostol and 8 intramuscular prostaglandin trials concludes that neither intramuscular prostaglandin nor misoprostol are preferable to conventional injectable uterotonics as part of the active management of the third stage of labor.

Our study also demonstrates comparable efficacy of carboprost (125□g) and methylergometrine (250□g) for prevention of PPH with higher risk of side effects when carboprost is used. Besides, carboprost is expensive.

Combination of ergometrine and oxytocin (syntometrine) has been tried for PPH prophylaxis. On comparison with syntocinon 10 units, there is a trade off between greater side effects and somewhat fewer women with blood loss exceeding 500 mL with syntometrine [6]. Oral ergometrine has not proved as effective.

WHO conducted a large multicentric international trial in which orally administered misoprostol (600□g) was compared with oxytocin (10 IU) [8]. Postpartum blood loss of 1000 mL was significantly more common in women who received oral misoprostol. Misoprostol use was also associated with side effects like shivering, nausea, vomiting and diarrhea, which are all dose dependent. Misoprostol (400 □g) has been tried rectally to reduce the side effects but conclusions could not be drawn due to small sample size [9].

Active management of labor with uterotonic injection at the delivery of anterior shoulder significantly reduces the incidence of PPH both in high risk and low risk patients. Carboprost (125 □g) is no better than methylergometrine (250 □g) in terms of efficacy but side effects are significantly more with carboprost making methylergometrine the drug of choice, which in addition is cheaper. Carboprost, which is well known for its therapeutic role in PPH management, can be used for prophylactic purpose in hypertensive patients where methylergometrine is contraindicated.

Larger trials are needed using the 'fracture bedpan' for accurate, analysis of blood loss and meaningful conclusions.

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