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SAFETY, EFFICACY AND ADVANTAGES OF PROPHYLACTIC USE OF SINGLE DOSE OF INTRAVENOUS CARBETOCIN DURING CAESAREAN DELIVERY FOR PREVENTION OF PPH: AN OBSERVATIONAL STUDY AT A TERTIARY CARE HOSPITAL.

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ABSTRACT

Background: Postpartum Haemorrhage is the leading cause of maternal mortality and morbidity in India with 38 % maternal deaths caused by it. Although most healthy women can cope well with blood loss after birth, some do not, and this can pose a serious risk to their health and even life. To reduce blood loss after birth, the routine administration of a drug to contract the uterus (uterotonic) has become standard practice across the world. We have developed numerous drugs which can be given prophylactically to prevent PPH and each of them have some advantages and disadvantages. The newest one is Carbetocin which is a long-acting synthetic oxytocin analogue with half-life of 40 minutes. Uterine contractions occur in less than 2 minutes after a single intravenous dose of 100microgram of Carbetocin. The present study was done to analyse safety, efficacy, and advantages of the Carbetocin, when administered to pregnant women at the time of caesarean delivery as a prophylaxis post-partum haemorrhage. **Material and Methods:** 200 pregnant women admitted for delivery at tertiary care hospital, who underwent caesarean section, both elective and emergency were included in the study. Inj Carbetocin, heat stable preparation ,100 mcg was diluted in 10 ml distilled water and given slow IV over 1 minute to all pregnant women at the time of caesarean section immediately after delivery of baby. **Results:** 84% of women had no atonic PPH and did not need any additional uterotonic drug for PPH. Remaining 16 % women who needed additional drugs for control of PPH had one or more risk factors responsible for PPH **Conclusion:** Single dose of 100 mcg IV Carbetocin is a safe and good drug for prophylactic use in pregnant women undergoing caesarean section for prevention of atonic PPH. Side effects are very less, advantages are many and overall results are promising.

KEYWORDS : Carbetocin atonic PPH uterotonic oxytocin

INTRODUCTION

The incidence of Postpartum haemorrhage (PPH) in India is 2-4% after vaginal delivery and 6% after caesarean section. It is the leading cause of maternal mortality and morbidity worldwide and accounts for about 35 % maternal deaths worldwide.[1] In India, PPH is the leading cause of maternal death with the reported incidence as high as 38%.[2] Although most healthy women can cope well with blood loss after birth, some do not, and this can pose a serious risk to their health and even life. Prophylactic uterotonic drugs can reduce blood loss and are routinely recommended. There are several uterotonic drugs for preventing PPH, but it is still debatable which drug or combination of drugs is the most effective.[3]

Definition and Types of Postpartum haemorrhage

Obstetric haemorrhage is the most common and dangerous complication of childbirth. Traditionally, postpartum haemorrhage (PPH) has been defined as greater than 500 mL estimated blood loss associated with vaginal delivery or greater than 1000 mL estimated blood loss associated with caesarean delivery. Primary postpartum haemorrhage is bleeding that occurs in the first 24 hours after delivery, while secondary postpartum haemorrhage is characterized as bleeding that occurs 24 hours to 12 weeks postpartum. [4]

Drugs for prevention of postpartum haemorrhage

Oxytocin (IM/IV, 10 IU) is recommended as the uterotonic drug of choice. Oxytocin is a naturally occurring hormone that stimulates uterine contractions and is commonly used as a uterotonic. The half-life of oxytocin is short (4–7 min); therefore, both repeated doses and continuous infusion are acceptable. The WHO and other organizations recommend that oxytocin should be stored between 2-8C° to prevent degradation and loss of effectiveness.[5] In developing countries like India, especially in rural areas where maintaining cold chain is difficult, Oxytocin loses its potency and is not very effective in control of uterine haemorrhage. Prostaglandin is also a naturally occurring hormone; misoprostol, a prostaglandin E1 analogue, can be used orally, sublingually, vaginally, or rectally Furthermore, misoprostol has mild side effects, such as shivering and pyrexia. Ergot alkaloids act to contract the myometrium through calcium channel mechanisms; however, this also increases the incidence of side effects such as hypertension. Hence there is a need of heat stable drug which can be used preferably single dose and has prolonged action.

Carbetocin : Drug profile and use

Carbetocin is the newest kid in the array of uterotonic drugs which fulfils all the criteria. Carbetocin is a long-acting synthetic oxytocin analogue, 1-deamino-1-monocarbo-(2-O-Methyltyrosine)-oxytocin, firstly described in 1987. It has a half-life of 40 minutes (around 4–10 times longer than oxytocin) and uterine contractions occur in less than two minutes after intravenous administration of optimal dosage of 100 µg .[6]

A single dose of Carbetocin has been hypothesized to act as a 16 hours intravenous oxytocin infusion regarding the increase in uterine tone and the reduction of the risk of PPH in elective

caesarean section .[7]Side effects of Carbetocin are similar to oxytocin but much less and does not cause vasopressin mimicking effect like salt and water retention.

MATERIAL AND METHODS:

This is an observational study over a period of 2 years, conducted on 200 pregnant women who were admitted for delivery at a tertiary care hospital and underwent caesarean section, either elective or emergency, using convenience sampling method.

The following were the inclusion and exclusion criteria.

Inclusion criteria:

1. Women undergoing elective or emergency caesarean section for any reason both term and preterm.

Exclusion criteria:

1 Women in whom Injection oxytocin was used for induction of labour
2. Women having severe Pre-eclampsia or Eclampsia
3. Women having epilepsy
4. Women with deranged liver and kidney function tests
5. Women with major cardiovascular disorder

Inj Carbetocin, heat stable preparation ,100 mcg, diluted in 10 ml distilled water was given slow IV over 1 minute to all pregnant women at the time of caesarean section immediately after delivery of baby as prophylactic to prevent atonic postpartum haemorrhage.

Data collection tool

Blood loss after delivery of baby was measured by visual estimation method, by counting number of standard size mops soaked with blood. Side effects of the drug were noted if any. Patients were observed over next 24 hours for blood loss and additional uterotonic drugs were given in case of atonic post-partum haemorrhage.

Data was collected in terms of age of women, parity, emergency or elective section, risk factors in women causing PPH, amount of blood loss during caesarean section, additional uterotonic drugs used. Data was analysed for safety of the drug, efficacy of the drug and advantages of the drug.

RESULTS:

200 women were enrolled in the present study. All received IV Inj Carbetocin during caesarean section soon after delivery of the baby.

1.Age of women

Age of women	No of women
18 – 24 yrs.	11(5.5)
25 - 29 yrs.	80 (40)
30 – 34 yrs.	84 (42)
35 – 39 yrs.	23 (11.
Above 40 yrs.	2 (1)

Majority of women (82%) were between 25 to 34 yrs.

2.Parity of women

Parity	No of women
Primipara	92 (46)
Multipara	108 (44)

3.Risk factors of Postpartum haemorrhage

Risk factors for PPH	No of pregnant women
No Risk factor	164 (82)
1 risk factor	30 (15)
2 risk factors	5 (2.5)
3 or more risk factors	1 (0.5)

4.Elective and emergency casearean section

	No of pregnant women
Elective Section	92 (46)
Emergency section	108 (54)

No of pregnant womenElective Section 92 (46)Emergency section 108 (54)

5. Primary Postpartum Blood loss (Visual estimation)

Amount of blood loss	No of women
Less than 200ml	0
200 ml – 500 ml	167 (83.5)
More than 500 Upto 1000 ml	31 (15.5)
More than 1000 ml	2 (1)

6. Need of additional uterotonic medication in immediate postpartum period

A) 15 women needed one additional drug for control of PPH either Oxytocin, Methylergometrine, Misoprostol

Uterotonic drug needed	No of women
Oxytocin	8
Methylergometrine	5
Prostaglandin F2alpha	0
Misoprostol	2

B) 11 women needed 2 additional drugs both Inj Oxytocin and IV Methylergometrine for control of PPH
C) 6 women needed 3 or more drugs for control of PPH
a) 3 women needed Oxytocin infusion, IV methylergometrine and Oral Misoprostol
b) 1 woman was given IV oxytocin, IV methylergometrine and 125 mcg Prostaglandin 2alpha IM
c) 2 women were given all drugs IV oxytocin, IV Methylergo metrine, Inj Prostaglandin F 2alpha and T Misoprostol

7.Relation between no of women and uterotonic drugs given

Sr no	Additional uterotonic drug required	No of women
1	No drug	168 (84%)
2	1 drug	15 (7.5%)
3	2 drugs	11 (5.5%)
4	3 drugs	4 (2%)
5	4 drugs	2 (1%)

8.Side effects of Carbetocin Vomiting, nausea, headache, and flushing are the most common side effects seen after IV Carbetocin, however no major side effects were seen in our patients. Other adverse effects that were less commonly reported included shivering, heart disorders, dizziness, dyspnoea and pruritis.

9. Relation between additional uterotonic drug needed and risk factors in women for PPH

Sr No	Additional uterotonic drug required	No of women with 1 risk factor	No of women with 2 risk factors	No of women with 3 risk factors
1	1 Drug	10	3	2
2	2 drugs	8	3	0
3	3 drugs	0	3	0
4	4 drugs	0	0	2

Sr NoAdditional uterotonic drug requiredNo of women with 1 risk factorNo of women with 2 risk factorsNo of women with 3 risk factors11 Drug 103222 drugs83033 drugs03044 drugs 002 All women who needed additional uterotonic drug for control of PPH had one or more than one risk factor for PPH. Only those women with 3 risk factors needed 4 drugs for control of atonic PPH.

DISCUSSION:

The period during delivery of the baby and placenta is defined as the third stage of labour and is a critical time for the occurrence of PPH. [8]After the third stage of labour, haemostasis processes are activated. Contraction of the uterine muscles is the primary physiological process for

postpartum haemostasis and results from the actions of oxytocin and prostaglandins. The contractions of the smooth muscles of the uterus act like living ligatures and compress the spiral arteries leading to complete stoppage of bleeding. Failure of these physiological mechanisms lead to atonic postpartum haemorrhage. PPH has 19 identified risk factors: age ≥35 years , body mass index ≥30 kg/m^2, Asian ethnicity , parity of three or more, primiparity, multiple birth, history of PPH, hypertensive disorders ,pre-eclampsia, placenta previa, placental abruption, retained placenta, induction of labour, obstructed labour, episiotomy, instrumental labour, caesarean section, gestational age at delivery <37 weeks, chorioamnionitis, prolonged use of oxytocin, general anaesthesia, and conditions that cause increased distention of the uterus such as multiple gestation, polyhydramnios, fetal macrosomia, and uterine fibroids. The main component of effective PPH prophylactic management is the administration of uterotonics. Other interventions that help in prevention of atonic PPH are early umbilical cord clamping, controlled cord traction for earlier delivery of the placenta, and in certain cases, uterine massage. The World Health Organization (WHO) guideline for preventing PPH recommend the following interventions: use of uterotonics during the third stage of labour for all births, use of oxytocin (10 IU) as the uterotonic drug, controlled umbilical cord clamping in settings where skilled birth attendants are available, and late cord clamping.[9]

Carbetocin is a long-acting synthetic analogue of oxytocin with half-life of 40 minutes. After slow IV administration over 1 minute given soon after delivery of baby in caesarean section, it helps in rapid and firm and sustained contraction of the uterus and helps in early separation of the placenta. Most of the women (84%) did not need any additional uterotonic drug which proves that single dose of 100 mcg of IV Carbetocin is effective for prevention of PPH .7.5 % women needed additional 1 drug for control of atonic PPH. In the remaining 8.5% of women who needed 2 or more drugs for control of PPH had 2 or more risk factors for PPH.99.5 % women had blood loss less than 1000ml which is within the standard acceptable limit of blood loss for women undergoing caesarean section. There was no atonic PPH in women who had no risk factors for PPH This proves that Carbetocin is 100 % effective in prevention of atonic PPH in women having no prior risk factors for PPH. Only 2 women having blood loss 1200 ml had more than 3 risk factors associated with PPH.

In a study conducted by tertiary maternity hospital in Mexico, pregnant women with at least one risk factor for PPH it was found that blood loss exceeding 500mL was lower in women assigned to Carbetocin than in women assigned to oxytocin. The frequency of severe PPH did not differ between the two groups.[10]In a meta-analysis conducted by Erkan Kalafat et al it was found that Carbetocin is effective in reducing the need for additional uterotonic use and postpartum blood transfusion in women at increased risk of PPH undergoing caesarean delivery which is similar to results achieved in our study.[11]

Advantages of Carbetocin include single dose of 100 mcg needed, volume of drug to be injected is low only 1ml which is beneficial to patients in whom fluids to be given are restricted. Since dose of drug is fixed, there is lesser confusion amongst health care workers and low chances of errors as compared to oxytocin which has varying doses. The formulation being heat stable, there is no loss of potency and efficacy of drug remains same when temperatures are high as in tropical countries. Vomiting, nausea, headache, and flushing are the most common side effects seen after IV Carbetocin, however no major side effects were seen in our patients. Other adverse effects that were less commonly reported included shivering, heart disorders, dizziness, dyspnoea and pruritis.[12]Side effects of Carbetocin are similar to oxytocin but far less and it does not cause vasopressin like side effects such as water intoxication and salt retention which is a major concern with oxytocin.

CONCLUSION

Single dose 100mcg of heat stable Carbetocin given IV to pregnant women at caesarean delivery soon after delivery of baby is a good prophylactic uterotonic to prevent PPH. It is very effective in women who have no risk factors for PPH. In addition, it reduces need of additional uterotonics in women who have 1 or more risk factors for PPH. Side effects of Carbetocin are like oxytocin but quite less. A major advantage is that it does no cause salt and water retention like oxytocin and its potency is maintained at room temperature making it ideal and cost-effective drug for prevention of PPH.

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