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Original Research Article

Oxytocin infusion versus per rectal misoprostol in the prevention of primary post partum haemorrhage in mothers with severe preeclampsia and eclampsia undergoing caesarean section at a peripheral Medical College

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Abstract

Objective: To study if misoprostol is as effective and safe as the gold standard, oxytocin, in the prevention of primary post partum haemorrhage in patients with severe preeclampsia and eclampsia undergoing caesarean section.
Method: One hundred patients with severe preeclampsia and eclampsia scheduled for caesarean section were recruited in a prospective randomized interventional trial to receive either oxytocin infusion (10IU in 500 ml Ringers lactate at 100cc/hr) or 600 µg per rectal misoprostol after delivery. Blood loss in 24 hrs after delivery, haemoglobin and haematocrit before and 24 hrs after delivery, need for additional oxytocic therapy and incidence of side effects were noted.
Results: The mean blood loss (P = 0.712), drop in haemoglobin (P = 0.294), haematocrit (P = 0.768) and need for additional carboprost (P = 0.749), even though slightly higher in the group receiving misprostol, were not statistically significant. The incidence of shivering (P = 0.011) and fever (P = 0.044) were significantly more in the misoprostol group. These were however self limiting and mild.
Conclusion: Misoprostol can be used as an effective alternative to oxytocin where availability and storage of the latter is difficult and its side effects were not serious.
Keywords: Postpartum Haemorrhage, Severe preeclampsia, eclampsia, misoprostol, oxytocin.

1. Introduction

Post Partum Haemorrhage (PPH) is the most common cause of maternal mortality in the world [1]. In developing countries postpartum haemorrhage is a leading cause accounting for 25-43% maternal deaths [2]. According to WHO, 25.7% of worldwide maternal death takes place in India and two third of these occur after delivery, PPH being the most commonly reported complication[3]. Incidence of life threatening PPH has decreased following the widespread adoption of active management of third stage of labour (AMTSL). Prophylactic intramuscular oxytocin is the only evidence based component of AMTSL.

Primary PPH is defined as blood loses over 500 ml or more from the genital tract within 24 hours of the vaginal birth of a baby or 1000 ml or more after a cesarean delivery [4]. Among various causes, uterine atony is the most common cause of primary PPH and accounts for almost 70% of cases[5-7].

It is estimated that approximately 500-1000ml/mint blood perfuses the maternal uterus at term. So, cesarean section delivery inevitably result in significant post partum blood loss before the uterine musculature can contract around uterine spiral arteries. Non elective cesarean section deliveries have a higher risk of PPH than women who are delivered electively.

Severe Preeclampsia is defined as the presence of one or more of the following symptoms and signs [8]:

1) Systolic blood pressure of 160 mm Hg or higher, or diastolic blood pressure of 110 mm Hg or higher on two occasions at least 4 hours apart while the patient is on

bed rest (unless antihypertensive therapy is initiated before this time)

2) Thrombocytopenia (platelet count less than 100,000/microliter)
3) Impaired liver function as indicated by abnormally elevated blood concentrations of liver enzymes (to twice normal concentration), severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by alternative diagnoses, or both
4) Progressive renal insufficiency (serum creatinine concentration greater than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease)
5) Pulmonary edema

1.1 New-onset cerebral or visual disturbances

The ACOG has removed massive proteinuria (>5g) and fetal growth restriction from the definition of severe preeclampsia.

There is physiological expansion of intravascular volume in pregnancy. However, this is minimal or completely absent in patients with severe preeclampsia. This limited blood expansion is probably the result of generalized constriction of the capacitance vessels. The reduced plasma volume results in haemoconcentration as the disease progresses. After delivery the plasma volume increases and the haemoglobin and haematocrit values decrease because of decreased vasospasm, excessive blood loss during delivery and mobilization of extracellular fluids into the intravascular compartment. This plasma contraction coupled with preexisting physiological anaemia complicates matters and potentiates the effects of PPH.

Women with preeclampsia have a 1.53 fold risk for post partum haemorrhage [9]. It is estimated that about 5.8% of mothers with severe preeclampsia subsequently develop eclampsia [10].

Eclampsia is defined as seizures that cannot be attributable to other causes in women with preeclampsia. Newer onset of grand mal seizures in women with preeclampsia is considered to have eclampsia. It is a major predictor of cerebral haemorrhage and if not treated quickly it can lead to maternal death.

Magnesium sulphate is the drug of choice for seizure prophylaxis in patients with severe preeclampsia. It has some tocolytic effect, reduces platelet activation and prolongs bleeding time. These mechanisms implicate it in causing PPH.

Definitive treatment of severe preeclampsia and eclampsia is termination of pregnancy i.e. delivery of the foetus, after administration of magnesium sulphate. Pregnancy beyond 34 weeks of gestational age should be terminated promptly. So, numbers of nonelective cesarean section deliveries are more common in these patients.

Although oxytocin is the gold standard drug for prevention and treatment of primary PPH, it requires cool storage, sterile equipment, and trained personnel, hence routine use of oxytocin in low-resource settings may be difficult [11]. Misoprostol, a synthetic prostaglandinE1, has certain advantages over oxytocin. It is stable at room temperature, cheap, has variable routes of administration and storage is easier. In this Context, the present study was undertaken to compare the efficacy of per rectal misoprostol Tablets and I.V oxytocin infusion to prevent primary PPH in mothers with severe preeclampsia and Eclampsia undergoing cesarean section.

2. Materials and methods

After obtaining clearance from Clinical Research Ethics Committee, Burdwan Medical College and Hospital, this prospective randomized interventional study was conducted from March 2017 to February 2018 in the department of Gynaecology and Obstetrics, Burdwan Medical College and Hospital, Bardhaman, West Bengal, India.

2.1Ethical consideration

This study was conducted with full compliance to the declaration of Helsinki 2013[12]. The informed consent for participation in the study was obtained from the subjects whose age was above 18 years (considered adult in India). Where age of the subject was <18 years, consent was obtained both from the subject and their legal guardian. The aim and procedure of the study was described to the subjects in detail.

2.2 Subject recruitment

Subjects were recruited from the high risk and eclampsia ward in the department of obstetrics and gynaecology, Burdwan Medical College and Hospital. Patients with severe preeclampsia (according to the aforementioned criteria) and eclampsia undergoing caesarean section (CS) were included in the trial. Blood Pressure was measured by a standard mercury sphygmomanometer. Those with severe pre eclampsia or eclampsia undergoing CS for any other obstetric indication (Breech presentation, obstructed labour, post & repeat cesarean section, multiple pregnancies, placenta praevia, grand multipara and HELLP syndrome) were excluded as these had individual effects on PPH (Figure 1). Patients with known hypersensitivity to prostaglandins and history of coagulation disorder were also excluded.

Patients were assigned randomly to one of the two groups of 50 each. The first group (Group O) received 10 IU infusion of oxytocin (CIRON drugs and pharmaceuticals, Figure 2) in 500 mililiter Ringers lactate solution at the rate of 1,000 cc/h after delivery (First three bottles). The 2nd group (Group M) received placebo (distilled water) in Ringer lactate at the same rate plus 600µg per rectal misoprostol tablet (SYNOCHEM Pharmaceuticals, Figure 3).

Figure 1: Subject recruitment procedure

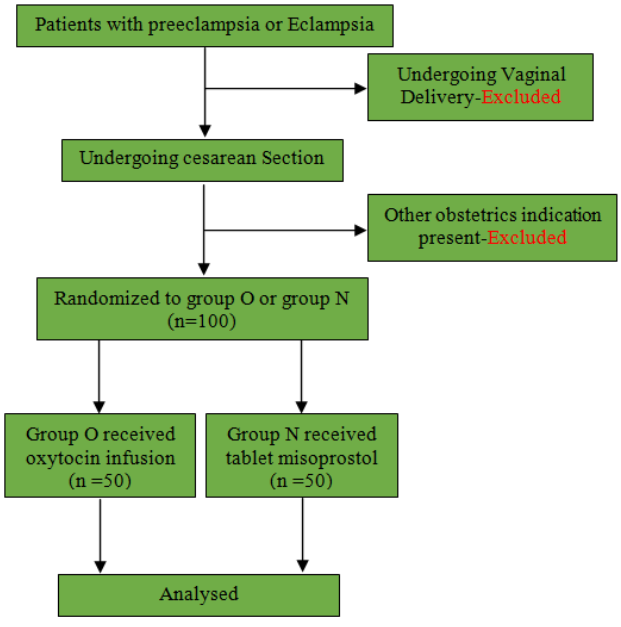

Figure 2: Oxytocin vial

Figure 3: Misoprostol strip

The main outcome measures were the determination of blood loss after delivery of placenta, change in haemoglobin levels, haematocrit drop, need for additional oxytocics, and drug-related side effects. Estimation of the amount of blood loss during cesarean section was done by subtracting the weight of blood soaked drapings and mops use during operation with preweighted dry drapings and mops before operation. The volume of blood in the suction bottle was also measured.24 hours postpartum blood loss was estimated by subtracting the weight of blood soaked sanitary vulval pads, used during 24 hours of postpartum period from preweighted dry sanitary vulval pads. The blood loss was estimated from weight gain 1gm≈1ml and blood-soaked sponges were measured. Heamoglobin values were determined both before surgery and 24 hr following surgery. The need for additional oxytocic therapy, operating time, need for blood transfusion, side effects of study drug, and any significant puerperal morbidity were also recorded. Haematocrit values were checked just before and after 24 hours of postpartum. The need for additional oxytocic therapy; operating time and side effects were noted.

2.3 Statistical Methods

Statistical analysis was carried out in GrapPad prism version 6.01 (GraphPad Software, La Jolla, CA, USA). Continuous variables were tested for normal distribution by the Kolmogorov–Smirnov test. Parametric data were expressed as mean and standard deviation (SD) and analysed by independent T test and Anova test. The $\chi 2$ test was used to analyse the incidence of side effects. A *P* value <0.05 was considered as significant, statistically.

3. Results and analysis

A total of 104 patients were recruited out of which 4 were excluded due to certain aspects violating the protocol.

There was no statistically significant difference in the demographic parameters between the two groups as seen in Table 1 (Age, Educational status and Residential area).

Table 1: Demographic details of the study subjects in two intervention group

	Subjects treated with		
	Oxytocin (*n*=50)	Misoprostol (*n*=50)	*P Value*
	Mean ± Standard Deviation		
Age	22.08 ±5.51	22.02 ±5.70	0.957
Educational status	Number (Percentage)		
Up to primary	11(22)	9(18)	0.61
Up to secondary	14(28)	16(32)	
Up to higher secondary	19(38)	15(30)	
Graduation and above	6(12)	10(20)	
Residential area			
Rural	38(76)	36(72)	0.648
Urban	12(24)	14(28)	

Table 2 showed there was no significant difference between the gravida of the subjects in the two groups. This is important as it is an individual parameter in the causation of PPH (Multigravid mothers have an increased risk of PPH [13]).

There was no statistically significant difference in the gestational age of mothers in the two groups as seen in Table 3. Operating time was also not significantly different between the two groups (Table 4).

Table 2: Gravida

Parameter (Gravida)	Subjects treated with		*P* value
	Oxytocin (*n* = 50)	Misoprostol (*n* = 50)	
	Number (Percentage)		
First	30(60)	29(58)	0.876
Second	11(22)	10(20)	
Third	11(23)	10(21)	

Table 3: Gestational Age

Parameter (Gestational Age)	Subjects treated with		*P* value
	Oxytocin (*n* = 50)	Misoprostol (*n* = 50)	
	Number (Percentage)		
<37 weeks	37(74)	34(68)	0.509
>37 weeks	13(26)	16(32)	

Table 4: Operating time

	Subjects treated with		
	Oxytocin (*n*=50)	Misoprostol (*n*=50)	*P Value*
	Mean ± Standard Deviation		
Operating time (min)	35.23 ±2.5	34.95 ±1.82	0.523

The main outcome parameters were blood loss, fall in haematocrit and haemoglobin levels in 24 hours and need for additional ecbolics, namely carboprost (PGF2α).

Table 5 shows no statistically significant difference in blood loss in the first 24 hours although it was slightly higher in the group receiving misoprostol.

Although the falls in haematocrit and haemoglobin levels are more in patients receiving misoprostol, there was no significant difference (Table 6 & 7)

Additional carboprost was needed in 5 patients receiving oxytocin infusion and 6 patients receiving misoprostol (Table 8). This difference was not statistically significant.

Table 5: Estimated blood loss in 24 hours postpartum period

	Subjects treated with		
	Oxytocin (*n*=50)	Misoprostol (*n*=50)	*P Value*
	Mean ± Standard Deviation		
Blood loss (ml)	807.40 ±205.17	822.40 ±199.29	0.712

Table 6: Haematocrit drop in 24 hours

	Subjects treated with		
	Oxytocin (*n*=50)	Misoprostol (*n*=50)	*P Value*
	Mean ± Standard Deviation		
Haematocrit drop (%)	7.86 ±2.05	7.98 ±2.00	0.768

Table 7: Haemoglobin drop in 24 hours

	Subjects treated with		
	Oxytocin (*n*=50)	Misoprostol (*n*=50)	*P Value*
	Mean ± Standard Deviation		
Haemoglobin drop (g/dl)	1.07±0.13	1.15±0.52	0.294

Table 8: Need for additional oxytocics

	Oxytocin (*n*=50)	Misoprostol (*n*=50)	*P Value*
	Number (Percentage)		
YES	5(10)	6(12)	0.749
NO	45(90)	44(88)	

The safety profile of the drugs (Table 9) showed that there were significantly higher complaints of shivering and fever in the misoprostol group. There were 3 patients who complained of mild chest discomfort after receiving oxytocin. There was no statistically significant difference in incidence of nausea and vomiting between the two groups.

Table 9: Side Effects

	Subjects treated with		
	Oxytocin (*n*=50)	Misoprostol (*n*=50)	*P Value*
	Number (Percentage)		
Nausea and Vomiting	4(8)	6(12)	0.739
Fever	3(6)	11(39)	0.044
Shivering	1(2)	10(20)	0.011
Chest pain	3(6)	0(0)	0.241

4. Discussion

This study was performed to assess whether misoprostol can be used as an alternative to oxytocin which has been the gold standard for PPH prevention. Our study showed that there was no significant difference in the efficacy between the two drugs. Per rectal route of misoprostol was chosen as incidence of side effects are more when it is administered orally. Patients with severe preeclampsia and eclampsia have an increased risk of PPH. Along with their (preeclampsia and eclampsia) inherent complications, PPH can cause devastating effects. This is due to the existing widespread haematological disturbances like contracted intravascular volume. Hence effective prophylaxis of haemorrhage is an essential component in the management of these patients.

The management of these hypertensive patients includes seizure prophylaxis and urgent delivery as the main pathology lies in the placenta. Caesarean section is performed commonly the time required inducing and augment labour may prove detrimental to the general condition of the patients.

In our study, additional ecbolics were needed in 11 patients (11%) with no significant difference between the groups. In Vimala *et al* [14] study it was 8.3%, 23% in Gerestenfeld and Wing [15] study and 30% in Mansouri and Alsahly study [16].

There were no cases with blood loss more than 1litre.This is in contrast to the Mansouri and Alsahly study [16] where 2 patients suffered from blood loss more than 1000 ml.

Adanikin *et al*[17] found mean immediate four hours post operative blood loss was not significantly different between the rectal misoprostol group (100.08

±24.85 ml), oxytocin infusion group (108.20±29.93 ml). The change between preoperative and post operative haemotocrit was similar in both groups. This is similar to our study.

Our study also resembles those presented by Vagge *et al* [18] where they found no significant difference between per rectal misoprostol and I.V. oxytocin group in term of mean blood loss, haemoglobin deficits and haematocrit deficits. Incidence of PPH was similar in both group. But shivering, fever and nausea were more common in misoprostol group than oxytocin group; but these side effects were mild and self limiting.

With respect to adverse effects, we found that misoprostol caused more shivering and fever which was statistically significant. This is similar to some previous studies [19, 20]. However there were certain studies where these side effects were not significant.

6. Conclusion

On the basis of the findings of this study, it would be fair to conclude that misoprostol is an effective alternative to oxytocin in the prophylaxis of PPH in patients with severe preeclampsia and eclampsia undergoing caesarean section. Although the incidence of side effects is higher, these are minor and self limiting. In rural hospitals where availability and storage of oxytocin may be a challenge, misoprostol can be a practical substitute

Limitations of the study

This study has several limitations. Subjects were recruited from a single hospital. Only subjective symptoms were used to determine the adverse effects. Caesarean sections under both regional and general anaesthesia were clubbed together. Evaluation of exact amount of blood loss was not possible.

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