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Original Research Article

A randomized controlled trial of sublingual Misoprostol (600µg) versus intravenous Oxytocin (10IU) in prevention of post partum hemorrhage during cesarean section

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ABSTRACT

Background: Mortality related to pregnancy and childbirth causes half a million women around the world to die annually. About 35% of these deaths are from postpartum hemorrhage (PPH). Prevention of PPH has been advised by the WHO by the use of Oxytocin 10 IU IM or IV and Misoprostol 600 µg in low resource settings in vaginal delivery. However there have been only a few reports on the use of Misoprostol during cesarean section. The best route and dose of Misoprostol is still being debated.

Methods: One hundred women with term singleton pregnancy undergoing elective or emergency cesarean section under spinal anesthesia were randomly allocated to receive either Misoprostol 600µg sublingually or intravenous oxytocin 10 IU soon after delivery of the baby. Estimated blood loss and comparative change in preoperative hemoglobin to post operative hemoglobin levels and side effects were evaluated.

Results: Blood loss was found to be more in Misoprostol than Oxytocin. Eight patients of the Misoprostol group required additional oxytocics. Oxytocin group did not receive any additional drugs. No surgical intervention was made in either of the groups. The most common side effect with Misoprostol was shivering (46%) and in Oxytocin group fever (4%).

Conclusions: Sublingual Misoprostol of 600µg works to prevent postpartum bleeding. In our study Oxytocin was more effective than Misoprostol in preventing PPH during cesarean section. Late onset of action of Misoprostol in comparison to Oxytocin may render suturing of the uterus difficult due to pooling of blood. In settings in which use of Oxytocin is not feasible, Misoprostol might be a suitable alternative for post-partum hemorrhage.

Keywords: Blood loss, Cesarean section, Hemoglobin, Misoprostol, Oxytocin, Post partum hemorrhage

INTRODUCTION

Postpartum hemorrhage (PPH) is the leading cause of maternal mortality, accounting for about 35% of all maternal deaths.[1] Every year about 14 million women around the world suffer from PPH worldwide.[2] The traditional definition of primary PPH is the loss of 500ml or more of blood from the genital tract within 24 hours of the birth of a baby. PPH can be minor (500-1000ml) or major (more than 1000ml). Major could be divided to moderate (1000-2000ml) or severe (more than 2000ml).[3] Since, it is difficult to accurately measure blood loss the true incidence of PPH may be underestimated by up to 50%. Most PPH cases occur in the immediate postpartum

period-within 24 hours after birth (primary PPH), and are due to uterine atony. Without immediate and proper medical attention, a woman with PPH can die.[4]

When postpartum hemorrhage occurs, a number of medical and surgical interventions are used to control the bleeding. The most commonly used agents are Oxytocin, Ergometrine and Misoprostol and Prostaglandin F2 - Alpha. Oxytocin, which has been used routinely for many years, is considered the drug of choice for preventing postpartum hemorrhage because it produces the fewest side effects.[5] Syntometrine, which combines the rapid onset of action of oxytocin and the prolonged action of ergometrine, is an alternative.[6,7] Prostaglandins (e.g., carboprost, sulprostone) are strong uterotonic third-line agents used in intractable postpartum hemorrhage when fundal massage and use of other oxytocics fail.[8,9]

None of these oxytocics are stable in light or in high ambient temperatures and therefore require refrigeration for maintenance of the "cold chain." They also should be protected from freezing.[10,11] Further, these agents require parenteral administration.[12]

Misoprostol (15-deoxy-16-hydroxy-16-methyl PGE1), a prostaglandin E1 derivative, has been investigated as an alternative to conventional parenteral uterotonics for PPH where resources necessary for effective uterotonic (e.g. oxytocin) administration are scarce.

Misoprostol can be given sublingually, rectally, intrauterine, orally. Doses vary from 200 to 1000µg. Sublingual Misoprostol has the shortest time to peak concentration, highest peak concentration and greatest bioavailability in comparison to oral, vaginal, buccal and rectal rotes. The mean time to increase the tone of the uterus is 8mins and 11 mins respectively for sublingual and oral route and 20 mins for vaginal route. The peak concentration is by 30 minutes for both oral and vaginal routes.

Misoprostol is an inexpensive drug and easily available. It is easy to use and does not require special storage conditions i.e., can be stored easily at room temperature; is thermostable and light stable; does not require specific conditions for transfer and has a shelf life of several years. These advantages make it a useful drug in reducing the incidence of postpartum hemorrhage in developing countries. It causes side effects like shivering, pyrexia and diarrhea.[13]

The aim of the study was to compare the effectiveness and safety of sublingual misoprostol with intravenous oxytocin administered after delivery in reducing blood loss at cesarean section.

The following are the objectives of this study;

- The primary outcome is to compare effectiveness of sublingual Misoprostol (600µg) to intravenous Oxytocin (10 IU) for prevention of postpartum hemorrhage during cesarean section by measuring intraoperative blood loss.
- Secondary outcome is to compare change in preoperative hemoglobin to post operative hemoglobin levels and study side effects of sublingual misoprostol (600 µg) and intravenous oxytocin (10 IU).

METHODS

Source of data

This study was carried out in Department of Obstetrics and Gynecology, BLDE (Deemed to be) Shri B.M. Patil Medical College, Hospital and Research Centre, Vijayapura, Karnataka, India. The study commenced on from 1st May and ended by 30th June 2012. The Study population consisted of South Indian women of lower socio-economic status. The study design is an open label randomized control trial. A total of 100 participants were included in the trial.

The study was approved by the institute's ethical committee.

Inclusion criteria

- Women with singleton pregnancies of 37-42 weeks of gestation undergoing cesarean section under subarachanoid block were included in the study.

Exclusion criteria

- Women suffering from coagulopathy, prior myomectomy, chorioammionitis, ante partum hemorrhage, severe anemia, thrombocytopenia, multiple gestations and previous caesarean section were excluded from the study. Patients who were hypersensitive to prostaglandins and bronchial asthmatics were also excluded.

The method of randomization

- After fulfilling the eligibility criteria, written and informed consent was taken. Details of the trial regarding the drugs used and their side effects were explained.

Detailed history, examination and investigations, were obtained from each woman participating in the study. By using computer generated random numbers, each participant was allotted to either Misoprostol or Oxytocin group. These numbers were placed in opaque sealed envelopes. The envelopes were opened in sequence in operating theatre, just before the start of surgery and note shown to the surgeon and anesthesiologist.

- Subarachanoid block was given. Lower segment cesarean section was performed. After clamping cord

of baby, women in misoprostol group were asked to hold 3 tablets of 200 microgram misoprostol under tongue; they shall swallow remaining bits after 20 min.

After clamping cord of the baby, women in oxytocin group received an intravenous infusion of 10IU of oxytocin in 500ml Ringer lactate.

- Intra operative blood loss was measured by weighing the soaked mops and blood collected in suction jars. Blood soaked mops were weighed in grams and the known dry weight of mops was subtracted, this volume was added blood collected in suction jars. Per vaginal clots or blood were collected and recorded.

- Hemoglobin levels on the day of surgery or within 1 week of surgery were recorded. Hb levels were recorded 72 hours ±6hours of the surgery and the difference was noted.

- Side effects were noted like elevated temperature, shivering, nausea, vomiting, diarrhea and others were recorded for 3hours after surgery.

Statistical analysis

A total of 50 women received 600µg of sublingual Misoprostol and another 50 women received 10 IU Oxytocin infusion for the treatment of primary PPH. All characteristics were summarized descriptively. For continuous variables, the summary statistics of mean± standard deviation (SD) were used to analyze the age, parity , mean blood loss , blood loss range and drop in the pre op and post operative Hemoglobin levels. For categorical data, the number and percentage were used in the data summaries and diagrammatic presentation. Chi-square ($\chi 2$) test was used for association between two categorical variables. The difference of the means of analysis variables between two independent groups was tested by unpaired t test. If the p-value was < 0.05, then the results were considered to be statistically significant otherwise it was considered as not statistically significant. Data were analyzed using SPSS software v.23.0, and Microsoft office 2007.

RESULTS

A total of 50 women received 600µg of sublingual Misoprostol and another 50 women received 10 IU Oxytocin infusion for the treatment of primary PPH.

In this study, the maximum age on the participating women was 35 years and the minimum age was 18 yrs. There was no significant difference in age between the two groups. (Table 1) The maximum parity was found to be 2 and minimum was 1. No significant difference change in parity between the two groups (Table 2). Blood loss was found to be more in Misoprostol (750ml) than Oxytocin (630ml) (Table 3).

Table 1: Comparison between Oxytocin and Misoprostol with respect to age.

Intervention	Mean age	SD	P-value	Remarks
Oxytocin	23.44	3.34	0.74	Not significant
Misoprostol	23.22	3.31		

Data presented as Mean age, SD (Standard Deviation), Chi-square ($\chi 2$) test used for calculating the P value, the p-value was > 0.05, and hence the results are considered to be statistically insignificant.

Table 2: Comparison between parity in Oxytocin and Misoprostol group.

Intervention	Mean parity	SD	P-value
Oxytocin	1.16	0.14	0.568
Misoprostol	1.10	0.34	

Data presented as Mean parity, SD (Standard Deviation), Chi-square ($\chi 2$) test used for calculating the P value, the p-value was > 0.05, hence the results are considered to be statistically insignificant.

Table 3: Comparison between Oxytocin and Misoprostol with respective blood loss.

Intervention	Mean blood loss in ml	SD	Minimum blood loss	Maximum blood loss	P-Value
Oxytocin	630.248	156.17	409	1265	<0.001 (highly significant)
Misoprostol	750.62	250.90	632	1424	

Data presented as Mean blood loss, SD (Standard Deviation), Chi-square ($\chi 2$) test used for calculating the P value, the p-value was < 0.05, hence the results are considered to be statistically significant.

However blood loss >1000 ml was higher in Misoprostol group as compared to oxytocin group, this questions the efficacy of Misoprostol in massive PPH (Table 4). Eight women in the Misoprostol group required additional oxytocic drugs. Additional drugs used were Oxytocin 10 IU, IM and IV route, Methyl ergometrine 0.2 mg. IV Oxytocin group did not receive any additional drugs. No surgical intervention was made in either of the groups. In our study was fall in hemoglobin in Misoprostol group than that of Oxytocin group. More women in Misoprostol group had drop of Hb >2.5gm% compared to women in oxytocin group. However majority of women had drop in

Hb <2.5gm% (Table 5). The most prevalent side effects following Misoprostol treatment was shivering (46%) and in oxytocin group fever (4%). Some of the women found an unpleasant taste when it is taken sublingually or buccally. A sense of numbness over the mouth and throat has also been reported when it is taken sublingually (Table 6).

Table 4: Distribution of blood loss in Oxytocin and Misoprostol.

Blood loss range	Oxytocin	Misoprostol
0-499ml	6 (12%)	6 (12%)
500-1000ml	42 (84%)	38 (76%)
1001-1500ml	2 (4%)	6 (12%)
Total	**50 (100%)**	**50 (100%)**

Table 5: Comparison between Oxytocin and Misoprostol with respective difference in hemoglobin concentration pre and post-operatively.

Difference in pre-op and post-op Hb	Oxytocin	Misoprostol
0-2.5 gm/dl	48 (96%)	36 (72%)
> 2.5gm/dl	2 (4%)	5 (10%)

Table 6: Comparison of side effects with Misoprostol and Oxytocin.

Drug	Shivering	Elevated temperature
Misoprostol	46 (92%)	0
Oxytocin	0	4 (8%)

None of the cases underwent any surgical intervention.

DISCUSSION

PPH is leading cause of maternal death. Prostaglandins have mainly been used for postpartum hemorrhage when other measures fail. Misoprostol, an inexpensive prostaglandin E1 analogue, has been suggested as an alternative for routine management of the third stage of labor.[14]

Misoprostol is safe, evidence based potent uterotonic, affordable, often easily available, easy administration. In places where Oxytocin is not available, Misoprostol play an important role in management of PPH.

In this study, it was observed that action of Misoprostol was inferior to Oxytocin. This has been studied in other studies.[13] Blood loss was more in Misoprostol group then that of Oxytocin. This was observed by Acharya et al as well.[15] Misoprostol is not effective if blood loss was >1000 ml. Additional drugs were used for 8 patients who received Misoprostol. Hemoglobin levels were decreased in Misoprostol group then that of Oxytocin group.

Eftekhari N et al, observed that the efficacy of sublingual Misoprostol is equivalent to that of low dose intravenous Oxytocin in reducing postpartum hemorrhage at caesarean section. Misoprostol has some other advantages like long shelf -life, stability at room temperature and oral use.[16]

In our study majority of the patients developed shivering and 4 women had pyrexia.

Misoprostol when administered in higher doses can produce headache, tremors, convulsions, nausea and vomiting, bradycardia, hypotension and sedation. Some of the side effects of subarachnoid block are headache, nausea and vomiting, bradycardia and hypotension and sedation which are similar to that of Misoprostol. According to Vimala N et al, observed that occurrence of transient side effects such as shivering and pyrexia were noted more frequently with the use of Misoprostol. Other studies has also noticed shivering and pyrexia as side effect.[17]

None of the cases in either oxytocin or misoprostol underwent surgical intervention.

CONCLUSION

Delayed action of Misoprostol led to pooling of blood in surgical field secondary to uterine atony this led to surgical hindrance during surgery on closure of the uterine walls by the surgeon. This may have caused increased blood loss. Timing of giving Misoprostol after clamping of the baby's cord may also led to the delayed desirable action. Our study observes that oxytocin is more effective than Misoprostol during cesarean section. Action of Oxytocin was faster than that Misoprostol.

Misoprostol can be used as an alternative drug where Oxytocin is not available.

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