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ORIGINAL ARTICLE

# A Comparative Study of Oxytocin/Misoprostol/ Methylergometrine for Active Management of the Third Stage of Labor

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**Abstract**

*Objectives* To study oxytocin, misoprostol, and methylergometrine in active management of the third stage of labor and determine duration of the third stage of labor, blood loss, adverse effects, and need for additional uterotonics in each group.

*Methods* Clinical trial of 300 women with healthy singleton pregnancy allocated into three groups to receive either: 10 IU intravenous oxytocin infusion, 600 μg sublingual misoprostol, or 200 μg intravenous methylergometrine. Primary outcome measure was blood loss in the third stage of labor; secondary measures were duration of the third stage, side effects, and complications.

*Results* Subjects who received 600 μg of misoprostol had the least blood loss, followed by oxytocin, and methylergometrine. The shortest mean duration of the third stage was with misoprostol. Shivering and pyrexia were observed in misoprostol group, and raised blood pressure in methylergometrine group.

*Conclusions* Misoprostol is as effective as oxytocin and both are more effective than methylergometrine in active management of the third stage of labor.

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## Introduction

Postpartum hemorrhage (PPH) has been a nightmare for obstetricians since centuries. In developing countries, PPH continues to be a leading cause accounting for 25–43 % of maternal deaths [1]. Atonic PPH is the most common cause of PPH and the leading cause of maternal death [2].

One intervention that has been promoted as an effective method in preventing atonic PPH is the active management of the third stage of labor [2]. By various studies conducted it has been proved that prevention of PPH can be achieved by active management of the third stage of labor in almost 40 % of cases [3].

Several drugs reduce PPH by stimulating the uterus to contract. Ergot derivatives have been used for decades; although oxytocin is the drug of choice, in some centers, methylergometrine is still being used. Several prostaglandins are used as the second- or third-line agents. These drugs, however, must be refrigerated to remain effective. Moreover, most uterotonics must be administered by injection; which requires sterile equipment and training in safe administration, prerequisites which are unavailable for most women delivering in poor undeveloped countries. Misoprostol, a prostaglandin E1 analog, is heat stable and can be administered orally, rectally, or sublingually. Most of the randomized studies of prophylactic misoprostol have

used oral and rectal administration, though a recent pharmacokinetic study showed that sublingual administration achieves the highest peak concentration and the best bioavailability [3].

The purpose of this study was to compare these most frequently used uterotonic agents in terms of their efficacy and side effects.

## Materials and Methods

The present study was conducted in the labor room of the Department of Obstetrics and Gynaecology, Government Medical College and Rajindra Hospital, Patiala. During the period 2010–2012, 300 pregnant women undergoing spontaneous or induced labor with intended vaginal delivery were included in the study. The women were selected according to the following criteria:

Inclusion criteria:

1. Low-risk singleton pregnancy
2. Gestational age $\geq$ 37 weeks
3. Parity $\leq$ 3

Exclusion criteria:

1. Any high-risk pregnancy
2. Previously scarred uterus
3. Instrumental delivery
4. History of manual removal of placenta in previous pregnancy

The cases were divided into three groups of 100 each.

- In Group I, 100 subjects were given oxytocin 10 IU intravenous infusion in 500 ml of Ringer's lactate immediately after the delivery of the baby.
- In Group II, 100 subjects were given 600 μg misoprostol sublingually after the birth of the baby.
- In Group III, 100 subjects were given 0.2 mg of methylergometrine intravenously after the delivery of the baby.

A kidney tray was kept pressed against the vulva of the woman with the cut end of the cord and blood loss was collected and measured with a measuring cylinder.

Placenta was delivered by controlled cord traction (Brandt Andrews' method).

After the delivery of the placenta duration of the third stage was noted in minutes. The placenta was inspected for its completeness and the total amount of bleeding measured after breaking the clots and cleansing the whole vagina and cervix of the clots.

Need for any additional uterotonic was noted in each group. Women were observed for PPH and any adverse effects.

Statistics

SAS software was used. ANOVA was applied for the comparisons.

## Results

The majority of subjects were in the age group of 20–24 years. The mean age in Group I (oxytocin group) was 24.94 ± 4.25 years, in Group II (misoprostol group) was 24.07 ± 4.01 years, and in Group III (methylergometrine group) was 23.71 ± 3.51 years. The difference in age between the three groups was not statistically significant.

Majority of subjects in all the groups were nulliparas, i.e., 46 % in Group I (oxytocin), 51 % in Group II (misoprostol), and 55 % in Group III (methylergometrine). The difference between the parity in the three groups was not statistically significant (Tables 1, 2).

Maximum number of subjects in all three groups were in the gestation age of 37–39 weeks. The mean gestational age in Group I (oxytocin group) was 38.68 ± 1.14 weeks, in Group II (misoprostol group) was 38.58 ± 1.08 weeks, and in Group III (methylergometrine group) was 38.76 ± 1.08 weeks. The difference between gestational age in the three groups was not significant.

Mean duration of the third stage of labor in the oxytocin group was 6.411 ± 1.589 min, while that in the misoprostol group was 6.128 ± 1.563 min and methylergometrine group was 7.191 ± 3.545 min. The difference

**Table 1** Baseline characteristics

| Characteristics | Oxytocin $n = 100$ | Misoprostol $n = 100$ | Methylergometrine $n = 100$ | Significance |
|---|---|---|---|---|
| Age (years) | 24.94 ± 4.25 | 24.07 ± 4.01 | 23.71 ± 3.51 | P = 0 .078 |
| Parity | Primiparae = 46 | Primiparae = 51 | Primiparae = 55 | P = 0.159 |
| | Multiparae = 54 | Multiparae = 49 | Multiparae = 45 | |
| Gestational age (weeks) | 38.68 | 38.58 | 38.76 | P = 0.493 |
| Birth weight (g) | 2,740.20 | 2,707.80 | 2,748.00 | P = 0.754 |

**Table 2** Studied characteristics

| Characteristics | Oxytocin $n = 100$ | Misoprostol $n = 100$ | Methylergometrine $n = 100$ | Significance |
|---|---|---|---|---|
| Third stage duration (min) | 6.411 ± 1.589 | 6.128 ± 1.563 | 7.191 ± 3.545 | Significant |
| Blood loss in third stage (ml) | 118.60 ± 70.72 | 101.45 ± 56.24 | 189.50 ± 90.65 | Significant |
| Need for additional uterotonics | 3 % | 1 % | 7 % | Non significant |
| Side effects | S = 3 | S = 23 | N = 23 | Significant |
| | N = 1 | F = 11 | V = 10 | |
| | H = 1 | V = 1 | S = 3 | |
| | | | H.T. = 2 | |
| Third stage complications | | PPH = 1 | PPH = 1 | Non significant |
| | | | Ret Placenta = 1 | |

*S* shivering, *N* nausea, *V* vomiting, *H* headache, *F* fever, *HT* hypertension

between oxytocin and misoprostol groups was not significant; both of these are equally effective in reducing the duration of the third stage of labor. Similarly, the difference between oxytocin and methylergometrine was not significant. However the difference between the duration of the third stage of labor was significant between the misoprostol and methylergometrine groups with a $p$ value of $<0.05$. Hence misoprostol was significantly more effective in reducing the third stage duration compared to methylergometrine. After oxytocin, misoprostol is the drug that should be considered for the prevention of PPH (Fig. 1).

Mean blood loss in Group I (oxytocin group) was 118.60 ± 70.72 ml and in Group II (misoprostol group) was 101.45 ± 56.24 ml, while in Group III (methylergometrine group) was 189.50 ± 90.65 ml. The difference was statistically significant in case of comparison of oxytocin–methylergometrine and misoprostol–methylergometrine groups, but not in oxytocin–misoprostol group. Misoprostol and oxytocin were more effective in reducing stage three blood loss compared with methylergometrine.

Additional uterotonics were needed in 3 % cases in the oxytocin arm, 1 % subjects in the misoprostol group, and

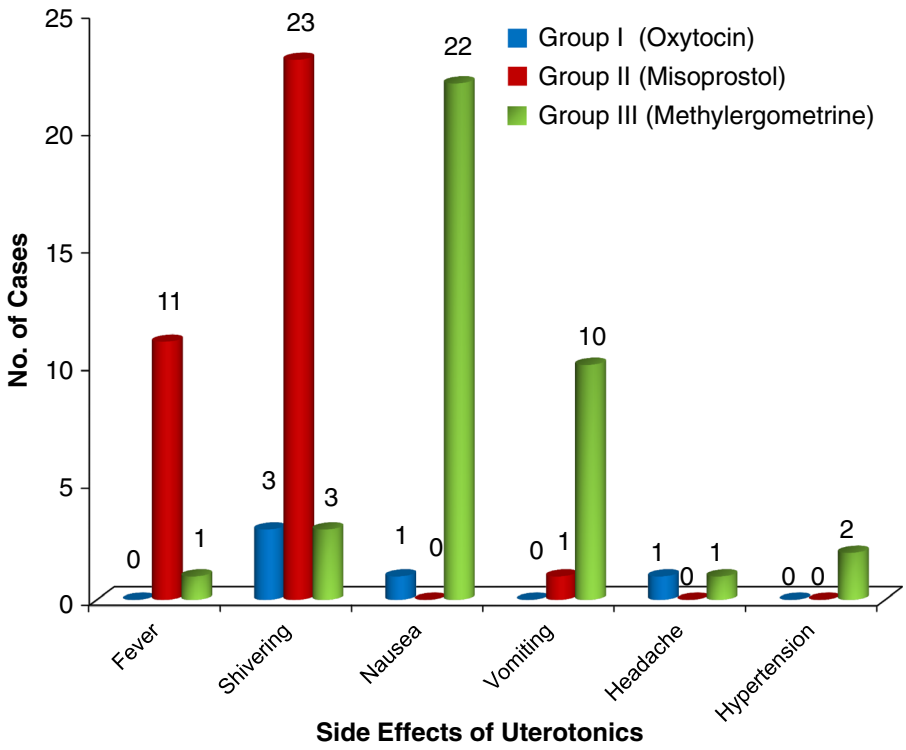


**Fig. 1** Side-effects

7 % in the methylergometrine group. The difference in three groups was insignificant.

We found no significant side effects in Group I (oxytocin group).

In Group II (misoprostol group), the main side effects were shivering (23 %) and fever (11 %). Misoprostol-induced shivering occurred in the immediate postpartum period and disappeared by itself. Shivering was sometimes associated with fever which recovered spontaneously after 1–2 h.

In Group III (methylergometrine group), the side effects seen were in the form of nausea and vomiting which occurred in 22 and 10 % cases, respectively.

Complications occurred in the form of retained placenta (1 % in the methylergometrine group) and PPH (1 % each in misoprostol and methylergometrine group). These were not significant when comparison was done.

No study subjects needed blood transfusion.

Mean birth weight was 2,740.20 ± 418.52 g in Group I (oxytocin group), 2,707.80 ± 428.49 g in Group II (misoprostol group), and 2,748.00 ± 353.11 g in Group III (methylergometrine group). The difference between the birth weights among the three groups was not significant.

## Discussion

According to WHO recommendations for prevention of PPH "active management of third stage of labor" should include administration of an uterotonic soon after birth of the baby, delayed cord clamping, and delivery of the placenta by controlled cord traction, followed by uterine massage [2].

Adequate storage and parenteral administration of an oxytocic by a trained health worker is not feasible in many developing countries including India. Misoprostol offers distinct advantages because it is stable at room temperature, affordable, and easy to administer.

The present study compared the duration of the third stage of labor, blood loss, and adverse effects of three oxytocic regimes. The sublingual route of administration of misoprostol was chosen in the present study because of better pharmacokinetics compared with oral or vaginal routes [4]. Sublingual tablets were easy to administer and well accepted by women.

Oral misoprostol has been found to have comparable results to standard parenteral oxytocics in reducing PPH [5–7]. However, conflicting results showing that misoprostol is less effective than traditional uterotonics have also been published [8]. A recent Cochrane meta-analysis concluded that misoprostol is better than a placebo but less effective than conventional parenteral oxytocics during active management of third stage of labor [9].

## Conclusion

We concluded that misoprostol is as effective as oxytocin and both of these are more effective than methylergometrine in the active management of third stage of labor.

Methylergometrine and oxytocin have special storage requirements with temperatures between 2 and 8 °C and have to be given parenterally; whereas misoprostol is stable at high temperature, has a shelf life of several years, and can be administered orally or sublingually.

Oxytocin is safest as far as side effects are concerned, whereas with misoprostol we observed side effects which settled with time without any treatment.

Hence if misoprostol is made available to the trained birth attendants, who supervise majority of the births in India, the lives of many women dying of atonic PPH can be saved.

In low-income countries, maternal anemia compounds the problem of PPH; therefore, administration of sublingual misoprostol could reduce maternal morbidity and mortality. Avoiding the intravenous or intramuscular route allows easier administration, and this could lead to widespread acceptance of active management of the third stage of labor. Any attempt to keep blood loss less than 100 ml would be a substantial intervention in low-resource settings where most women are anemic, and a blood loss of even 500 ml may have adverse effects.

These advantages of misoprostol make it a feasible drug to be used in the routine management of the third stage of labor.

**Conflict of interest** The authors have no conflicts of interest.

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