

Comparison of Rectal Misoprostol with IM Oxytocin in Prevention of PPH in Tertiary Care Hospital

*Dr. Praveena Gungam¹, Dr. Pruthvi Desireddy², Dr. Preethi Kola³,
Dr. Swathi Rapole⁴, Dr. V. Naga Jyothi⁵, Dr. Kasu Akshara⁶

^{1,2,3,4,5,6} Senior Resident, Dept. of Pharmacology, Osmania Medical College, Hyderabad, Telangana, India

Corresponding Author: Dr. Praveena Gungam

Abstract

Background: PPH, the leading cause of maternal death worldwide is almost entirely a preventable condition. The majority of these deaths occur within 4 hours of delivery, which indicates that they are a consequence of the third stage of labour.

Aims and Objectives: To compare the effect of Rectal Misoprostol and IM Oxytocin in prevention of post partum haemorrhage.

Patients and Methods: An open labelled, prospective, randomised observational study was carried out in GMH, Hyderabad. 200 pregnant women in active labour, fulfilling the inclusion criteria were enrolled for the study. As a part of active management of third stage of labour, 10 IU of IM oxytocin and 600 µg of rectal misoprostol were given to control and study groups of 100 each respectively. Paired t test to compare within the group and unpaired t test for intergroup analysis was used, with level of significance 0.05.

Results: Rectal misoprostol 600 µg is as effective as 10 IU intramuscular oxytocin in minimizing blood loss in the third stage of labour.

Conclusion: Misoprostol can be recommended for routine use as uterotonic in prevention of post partum haemorrhage in low resource settings, where storage conditions for oxytocin are not met and in the absence of skilled birth attendant.

Keywords: Maternal mortality, Misoprostol, Oxytocin, Post partum haemorrhage.

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I. Introduction

Postpartum haemorrhage is the most serious complication in obstetric practice. The greatest number of maternal deaths from haemorrhage is due to PPH, which is almost entirely a preventable condition. WHO defines PPH as blood loss of 500 ml or more in first 24 hours post partum.¹ Postpartum blood loss is difficult to evaluate especially in developing countries like India where most of the women are anaemic with poor reserve and these conditions are further aggravated by increased demand during pregnancy and blood loss during 3rd stage of labour.² PPH is the leading cause of maternal death worldwide, with an estimated mortality rate of 1,40,000 per year, or 1 maternal death every 4 minutes.³ PPH occurs in 5% of all deliveries and is responsible for a major part of maternal mortality.^{4,5} The majority of these deaths occur within 4 hours of delivery, which indicates that they are a consequence of the third stage of labour.^{6,7} Nonfatal PPH results in further interventions, iron deficiency anaemia, pituitary infarction (Sheehan's syndrome) with associated poor lactation, exposure to blood products, coagulopathy, and organ damage with associated hypotension and shock.⁸

Several strategies have reduced postpartum blood loss and the incidence of severe postpartum haemorrhage. Active management of third-stage of labour,⁹ including early cord clamping and controlled cord traction¹⁰ and administration of uterotonic drugs such as oxytocin,¹¹ with or without ergometrine, have been beneficial. Compared to expectant management, active management decreases the incidence of PPH by 70%.¹²

Current uterotonic drugs are far from ideal, particularly for routine use in developing countries. As many deliveries take place far from hospitals or medical facilities and are supervised solely by birth attendants, inexpensive drugs with simple routes of administration and long shelf life are needed. Most of the uterotonics require parenteral administration and maintenance of cold chain which is necessary for their potency, which is not always possible in some peripheral centres due to non availability of sterile needles, syringes or refrigerating equipment.¹² Misoprostol, a synthetic prostaglandin E1 analogue, is used widely for prophylaxis and treatment of peptic ulcer disease.¹³ It is rapidly absorbed after oral administration,¹⁴ has few side effects, is stable at room temperature, and is inexpensive. It stimulates uterine contractions, and has been used for

termination of pregnancy first and second trimesters, and induction of labour at term.¹⁵ Its use in the third stage of labour has also been investigated using oral or rectal route.

India, being a developing country with lack of storage facilities in remote areas, there is a need for uterotonics with equal efficacy and safety as that of routine uterotonics available. The purpose of the present study is to compare the safety and efficacy of rectal misoprostol with intramuscular oxytocin in prevention of postpartum haemorrhage.

II. Patients And Methods

2.1 Method of collection of data

An open labelled, prospective, randomised observational study was carried out in GMH, Hyderabad for the duration of six months. Approximately 200 pregnant women in active labour, fulfilling the inclusion criteria were enrolled for the study after approval from the institutional ethics committee and informed consent from the patients.

2.2 Inclusion criteria

1. Age group: 18-35 yrs.
2. Gestational age: 37 completed weeks
3. Singleton pregnancy with live fetuses
4. Spontaneous and instrumental vaginal deliveries with or without episiotomy.

2.3 Exclusion criteria

1. Patients undergoing caesarean section
2. Medical disorders associated with pregnancy
3. Coagulation abnormalities
4. Known hypersensitivity to prostaglandin administration

The women were randomly divided into study and control groups of 100 each. Control group received 10 IU of IM oxytocin, study group received 600µg of rectal misoprostol, immediately after the delivery of anterior shoulder, as a part of active management of third stage of labour. The outcomes were incidence of PPH, amount of blood loss, duration of labour, incidence of side effects, pre- and post- delivery haemoglobin and use of additional uterotonics. The main outcome measure was change in haemoglobin concentration, before to 24 hours after delivery. Differences in the Hb values before and 24 hours after delivery were estimated in each group. Blood loss was estimated in the third stage of labour by placing a plastic pan under the patients at the time of placental separation and the number, and weight of soaked pads at the time of episiotomy repair (volume in cc = weight in grams) were determined. Blood loss was quantified by the weight and number of soaked towels or by changes in Hb concentration or hematocrit value. The primary outcome was to objectively estimate the amount of blood loss. The haemoglobin concentration was recorded before delivery. A second Hb was estimated before discharge (24 hours post- partum). Differences in the Hb values before and after delivery were estimated in each group.

Secondary outcomes included length of labour, length of third stage of labour, need for additional uterotonics, estimated blood loss, transfusion and medication side effects. Duration of labour was obtained from **partograph**.

The data were analysed by using Graph pad prism 6.05 trial version. Paired sample test was used to compare the differences between the count variables at 5% level of significance.

Continuous variables such as age, parity, gestational age, duration of third stage of labour, amount of blood loss, drop in haemoglobin were presented as mean±standard deviation. Percentages were calculated for qualitative variables i.e. mode of delivery, fever, shivering, nausea and vomiting, blood loss >500ml, need for blood transfusion and additional uterotonic drugs.

III. Results

A total of 200 pregnant women in active labour, fulfilling the inclusion criteria were randomised to receive either 600µg Rectal Misoprostol, group 1 (n = 100) or 10 IU IM Oxytocin, group 2 (n= 100) immediately after the delivery of anterior shoulder, as a part of active management of third stage of labour during the study. The results obtained are:

Table 1: Comparison of mean±SD of demographic characters in group 1 and group 2

Variables	Group 1 (Rectal Misoprostol) (N=100) Mean ±Sd	Group 2 (Im Oxytocin) (N=100) Mean±Sd	P-Value
Age(Years)	22.19±2.7	22.39±2.6	*
Gestational Age (Weeks)	39.13±0.96	38.86±1.0	*

Parity	1.78±0.86	1.71±0.84	*
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- * indicates p value that is not significant, p >0.05
- ** indicates p value that is significant, p <0.05
- *** indicates p value that is highly significant, p <0.05

Table 2: Comparison of incidence of pph in group 1 and group 2

Variables	Group 1 (Rectal Misoprostol) (N=100)	Group 2 (Im Oxytocin) (N=100)
>500	6 (6%)	5 (5%)
<500	94 (94%)	95 (95%)

Table 3: Comparison of mean±SD of blood loss in group 1 and group 2

Blood Loss (ml)	Group 1 (Rectal Misoprostol) (N=100) Mean±Sd	Group 2 (Im Oxytocin) (N=100) Mean±Sd	P-Value
Immediate	164.5±70.14	160.0±67.64	*
Within 2 Hours	39.0±26.18	39.4±29.19	*
Total	203.5±91.06	199.4±92.5	*

- * indicates p value that is not significant, p >0.05
- ** indicates p value that is significant, p <0.05
- *** indicates p value that is highly significant, p <0.05

Fig 1: Comparison of mean±SD of pre and post delivery haemoglobin in group 1 and group 2



- * indicates p value that is not significant, p >0.05
- ** indicates p value that is significant, p <0.05
- *** indicates p value that is highly significant, p <0.05

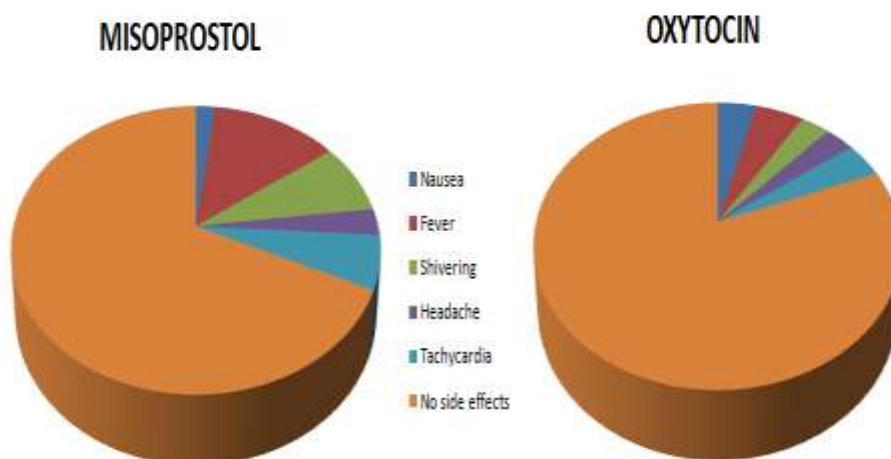
Table 4: Comparison of mean ± SD of duration of labour in group 1 and group 2

Length Of Labour	Group 1 (Rectal Misoprostol) (N=100) Mean ±Sd	Group 2 (Im Oxytocin) (N=100) Mean±Sd	P-Value
First Stage(Hours)	6.0 ±1.8	5.9±1.91	*
Second Stage(Hours)	0.43±0.26	0.5±0.29	*
Third Stage(Min)	4.1±1.28	3.97±0.83	*

Table 5: Comparison of use of additional uterotonics and blood transfusion in group 1 and group 2

Variables	Group 1 (Rectal Misoprostol) (N=100)	Group 2 (Im Oxytocin) (N=100)
Additional Uterotonics	15 (15%)	9 (9%)
Blood Transfusion	8 (8%)	7 (7%)

Figure 2 Comparison of side effects group 1 (Rectal Misoprostol) and group 2 (IM Oxytocin)



IV. Discussion

Active Management of Third Stage of Labour involving prophylactic administration of uterotonics, after the delivery of anterior shoulder, effectively decreases the incidence of post partum haemorrhage and improves maternal outcome. Conventional uterotonics used include oxytocin, ergometrine, syntometrine (which consists of 5 IU oxytocin [Syntocinon] and 0.5 mg ergometrine), prostaglandin F_{2α} and prostaglandin E₂. Oxytocin must be administered intramuscularly or intravenously, requires cold storage between 2°C to 8°C, lacks stability in tropical conditions.²⁷ Ergometrine has been ineffective when administered orally, ergot preparations require refrigeration and protection against light to preserve their effectiveness.²⁸ A variety of brands of ergometrine lost 21% to 27% of their potency after one month, and over 90% after one year of storage exposed to light and at 21°C to 25°C.²⁹ These storage requirements are an important hurdle to the widespread use of uterotonics in the developing world. Prostaglandins such as prostaglandin F_{2α} and synthetic prostaglandin E₂ derivatives are effective uterotonic drugs, but they are expensive and not storable at room temperature.³⁰ All these must be given by injection and are associated with side effects.

Misoprostol—a prostaglandin E₁ analogue registered for the prevention and treatment of peptic-ulcer disease. It has attracted widespread attention because of its strong uterotonic effects and ease of administration. These effects have been studied in early pregnancy, orally and vaginally after mifepristone for medical abortion,^{31,32} for cervical ripening before surgical termination of pregnancy,³³ and at term for induction of labour.³⁴ It is rapidly absorbed after oral administration, has few side effects, is stable at room temperature, and is inexpensive. Its use in the third stage of labour has also been investigated. The aim of the present study was to investigate whether misoprostol could prevent postpartum haemorrhage. Misoprostol was chosen as substitute for oxytocin to prevent postpartum haemorrhage, as it has similar advantages with minimal side effects. It is inexpensive and easily available. It is easy to administer and does not require special storage conditions (i.e., can be stored easily at room temperature; is thermo stable 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 haemorrhage in developing countries.

Rectal misoprostol is superior to oral route and can be considered as a uterotonic in the third stage of labour. The side effects are minimal while maintaining the uterotonic effects. The gastrointestinal side effects like nausea, vomiting, and diarrhea can be avoided with rectal route. Rectal route also has the practical advantage of ease of administration in the patients who are vomiting or unable to take orally or are under anaesthesia. Vaginal route of misoprostol has been used for termination of pregnancy but as this route is not feasible after delivery, rectal route was chosen. In the present study, Demographic characteristics like age, gestational age, mode of delivery, augmentation of labour are comparable in group 1 and group 2. Average amount of blood loss, incidence of PPH, pre and post delivery Hb, change in Hb, mean duration of labour are almost similar in both groups, with insignificant p value (p>0.05). Usage of additional uterotonics is more in group 1 as compared to group 2. Fever and shivering are more in group 1 compared to group 2 with significant p value. Nausea, headache and tachycardia are comparable in both the groups.

4.1. Incidence of PPH

In the present study, incidence of PPH (blood loss >500ml) is 6% in misoprostol group and 5% in oxytocin group. There is no significant difference in the incidence of PPH, with $p>0.05$. None of the patients in the study group had massive PPH defined as blood loss more than 1000ml. This was similar with World Health Organisation (WHO) multicentre randomised trial which compared 600 μ g oral misoprostol with 10 IU of intramuscular or intravenous oxytocin showed that blood loss was consistently higher in misoprostol group, with higher rates of blood loss more than 1000ml as compared to oxytocin group. Similarly misoprostol is also associated with increased use of additional uterotonics.²⁴ The finding of no case with blood loss more than 1000ml in the present study, is also consistent with that of a double blind placebo controlled randomised trial in which Walley et al. also reported no case of PPH more than 1000ml.⁵⁴

4.2. Average Amount Of Blood Loss

The reduction in blood loss is particularly important in our country where most of the child bearing population is anaemic. This reduction in blood loss reduces the incidence of post partum anaemia, infection and hence morbidity. Average blood loss in the present study is 203.5 \pm 91.06 for misoprostol group and 199.4 \pm 92.5 for oxytocin group. The comparison of blood loss between the two groups is not significant, with $p>0.05$. In S. Aziz, S. Kazi, G. Haq, et al.'s study,²⁹ average amount of blood loss was higher in misoprostol group than oxytocin group (302.86 \pm 160.4 vs 267.14 \pm 140.35; $p=0.236$) but it was not statistically significant. In Firouzbakht et al.'s study,²⁶ average amount of blood loss was 436.6 \pm 214.04 ml in misoprostol group and 415.06 \pm 227.2 ml in oxytocin group. The difference was not significant with $p = 0.069$.

4.3. Pre delivery and post delivery haemoglobin

In the present study, pre and post delivery haemoglobin (gm/dl) in misoprostol group are 10.14 \pm 0.83 and 9.0 \pm 0.88 respectively with change in haemoglobin 1.1 \pm 0.28. Pre and post delivery haemoglobin in oxytocin group are 9.9 \pm 0.58 and 8.7 \pm 0.6 with change in haemoglobin 1.1 \pm 0.33. The rate of drop of hemoglobin in the misoprostol group as compared to oxytocin group is not statistically significant with $p>0.05$. The pre and post delivery hemoglobin within misoprostol and oxytocin groups were statistically significant ($p<0.05$), whereas the pre-delivery and also the post-delivery hemoglobin between misoprostol and oxytocin were statistically not significant ($p>0.05$).

In S. Aziz, S. Kazi, G. Haq, et al.'s study,²⁹ the average drop in haemoglobin concentration (gm/dl) observed in oxytocin group was 1.55 \pm 0.38 vs. 1.66 \pm 0.61 in misoprostol group ($p=0.684$). Average drop in haematocrit (%) level though observed more in misoprostol group was insignificant between the two groups (4.18 \pm 0.64 vs. 4.50 \pm 0.92; $p=0.133$). In Firouzbakht et al.'s study,²⁶ pre delivery haemoglobin in misoprostol and oxytocin groups were 12.6 \pm 1.12 and 12.3 \pm 1.28 respectively, with p value 0.206. Post delivery haemoglobin in misoprostol and oxytocin groups were 11.8 \pm 1.03 and 11.53 \pm 1.34 respectively, with p value 0.28. Change in haemoglobin in misoprostol and oxytocin groups is 1.15 \pm 1.28 and 1.41 \pm 1.3 respectively, with p value 0.0468.

4.4 Average length of third stage of labour In the present study, average duration of third stage of labour (minutes) is 4.1 \pm 1.28 for misoprostol group and 3.97 \pm 0.83 for oxytocin group which is almost similar in both the groups.

4.5. Use of additional uterotonics

In the present study, the use of additional uterotonics in misoprostol group is 15% and 9% in oxytocin group. The use of additional uterotonics in misoprostol group is statistically significant, with $p<0.05$. This is comparable with the largest ever trial conducted by WHO on misoprostol use in third stage of labour involving >9000 women demonstrated higher proportion of women requiring additional uterotonic drugs.

4.6. Side effects

In the present study, fever, shivering and tachycardia are more in misoprostol group (13%, 4% and 6% respectively) with significant p value, $p<0.05$. Nausea and headache in oxytocin group are 4% and 3% respectively as compared to misoprostol group 2% and 3%. Fever and shivering after misoprostol is due to centrally mediated PGE1 effect associated with thermoregulatory physiology. Diarrhoea, most frequently seen with oral misoprostol is not reported in the present study with rectal misoprostol. These are comparable with other studies.

In Gohil et al.'s study,²⁸ Misoprostol caused significantly higher rate of pyrexia and shivering ($P = 0.01$ and 0.003) as compared to other drugs used in the study. Diarrhoea was also caused more frequently with misoprostol. However the difference was not statistically significant. In Shrestha et al.'s study,²⁷ an analysis of the side effects of the misoprostol and oxytocin revealed that fever with shivering was most frequent in misoprostol group (41%) as compared to oxytocin group (14%). They also noted abdomen pain in both

misoprostol as well as oxytocin group. They found these undesirable side effects of misoprostol to be self-limiting and shivering could be contained by simply covering the patient with blankets.

The reported incidence of shivering in WHO multicentre trial was 41% with a dose of 600µg and 37% with a dose of 400µg. Highly significant incidence of nausea, vomiting was not reported in the WHO multicentre randomised trial. Patted et al.³¹ mentioned in their study that misoprostol is associated with a significant increase in postpartum maternal shivering and fever.

The advantages of the rectal route of misoprostol are less gastrointestinal side effects like nausea, vomiting which are more common with oral route. Rectal route is advantageous especially in patients under anaesthesia and not able to tolerate orally. Shivering and hyperpyrexia were the most common side effects of misoprostol. However, none of the side effects were life-threatening or serious rather most of them subsided within 6–8 hours post partum and very few patients actually required some treatment to alleviate them. These side effects are acceptable and preferable to excessive bleeding. Given its proven efficacy for the prevention of postpartum haemorrhage, the benefits of misoprostol are greater than the associated risks.

4.7. Strengths and weaknesses of the study

The present study included subjects of different age groups in the reproductive age ranging from 15-45 years, The study also included subjects of different parity ranging from primipara to multipara with sixth gravida. It also included subjects with risk factors for post partum haemorrhage. Misoprostol 600µg was chosen on the basis of the initial report¹², that it might be more effective in reducing blood loss and probably postpartum haemorrhage than the 400µg dose, with similar rate of unwarranted side effects. In the present study, there was no significant difference in incidence of postpartum haemorrhage, though significant difference in blood loss and need for additional uterotonics was seen.

In the present study, women with twin gestation, a risk factor for post partum haemorrhage were not included. In the present study, subjects with risk factors needed additional uterotonics. An increase in dose of misoprostol in these cases would have reduced the need for additional uterotonics. There are studies with increased dose of misoprostol which have reported minimal side effects. Fauzia Anbreen et al.,²⁵ conducted a study with 800µg of rectal misoprostol for post partum haemorrhage with no severe side effects. In an uncontrolled study in which a single dose of 1000µg of misoprostol was prescribed for postpartum haemorrhage, no severe side effects were reported.³² In order to determine the dose in subjects with risk factors; studies must be done on a large population.

V. Conclusion

Misoprostol is a drug of low-cost, easy-to-administer, powerful uterotonic with an excellent safety profile and long shelf-life. Misoprostol has a revolutionary potential to reduce mortality and morbidity from postpartum hemorrhage. Misoprostol is safe and as efficacious as oxytocin in preventing PPH. Fever and shivering are more with misoprostol, compared to oxytocin. Rectal route is preferred as it is easy to administer by self, during home births without skilled birth attendant. It can be administered even in unconscious women and when oral route is not feasible due to nausea and vomiting. It can be recommended in low resource settings, where storage conditions for oxytocin are not met and in the absence of skilled birth attendant.

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