

## Oral misoprostol versus oxytocin in the management of third stage of labour

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### Abstract

**Objectives:** To compare oral misoprostol versus intramuscular oxytocin in the management of third stage of labour.

**Methods:** The quasi-experimental study was conducted at the Obstetrics and Gynaecology Unit II, Civil Hospital, Karachi, from June 20 to December 19, 2006. A total of 70 patients diagnosed in active phase of labour who fulfilled the inclusion criteria were selected by non-probability convenience sampling. These patients were divided into 2 groups of 35 patients each, for Oxytocin (Group 1) and misoprostol (Group 2).

Main and secondary outcome measures were analysed. SPSS 10 was used for statistical analysis.

**Results:** Average amount of blood loss(ml) was  $267.14 \pm 140.35$  with Oxytocin versus  $302.86 \pm 160.4$ , with Misoprostol, this difference was statistically insignificant ( $p=0.236$ ). Average drop in haemoglobin concentration (g/dl) with Oxytocin was  $1.55 \pm 0.38$  vs  $1.66 \pm 0.61$  with Misoprostol ( $p=0.684$ ). Drop in haematocrit (%) was  $4.18 \pm 0.64$  with Oxytocin vs.  $4.50 \pm 0.92$  with Misoprostol ( $p=0.133$ ). There was also insignificant difference in duration of third stage of labour, between oxytocin and Misoprostol groups ( $5.37 \pm 2.20$  vs.  $5.23 \pm 2.46$ ,  $p=0.451$ ) Shivering, in Misoprostol group occurred in  $n=11$  (31.4%) vs  $n=3$  (8.6%) with Oxytocin ( $p=0.017$ ) and pyrexia in  $n=6$  (17.1%) with misoprostol vs  $n=0$ , with oxytocin ( $p=0.025$ ) thus significantly higher in misoprostol group.

**Conclusion:** There were no major differences in oral misoprostol and intramuscular oxytocin in the management of third stage of labour.

**Keywords:** Postpartum haemorrhage, Third stage of labour, Active management of third stage, Misoprostol, Oxytocic drugs. (JPMA 64: 428; 2014)

### Introduction

Primary Postpartum haemorrhage (PPH) is defined as blood loss 500ml or more within 24 hours of delivery.<sup>1</sup> If such blood loss occurs from the genital tract after 24 hours and within first 6 weeks of delivery, then it is called Secondary PPH.<sup>2</sup> Massive PPH is defined as blood loss greater than 1000ml or 1500ml.<sup>3</sup> Laboratory parameters include a drop in haemoglobin of 4gm% and acute transfusion of more than 4 units of blood. Early and accurate assessment of blood loss is important to prevent delay in management and prevention of morbidity.<sup>4</sup>

In industrialised countries direct pregnancy-related mortality rate is 10/100,000 live-births<sup>5</sup> and of these 8% of deaths are caused by PPH, while in the developing part of the world maternal mortality rates are very high, specially in Africa and Asia. Maternal mortality rate in India is 560/100,000 live-births<sup>6</sup> and in Pakistan it is 276/100,000 maternities.<sup>7</sup> The incidence of primary PPH in developed countries is estimated to be 5 per cent of all deliveries.<sup>2</sup> The commonest cause of primary PPH is uterine atony accounting for 80 to 90% cases.<sup>1,8</sup>

Syntocinon is the synthetic form of octapeptide oxytocin.

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It can be administered intramuscularly or intravenously as continuous infusion. Half life of intravenously infused oxytocin is 3 minutes. It should not be used as a bolus as it causes a transient but marked fall in blood pressure followed by sudden rise in cardiac output which can be dangerous to already hypovolaemic women.<sup>9</sup> Syntocinon and its preservative chlorbutanol increase heart rate and have negative inotropic, antiplatelet and antidiuretic effect. Antidiuretic effect is responsible for water intoxication. It also causes nausea and vomiting. It requires storage at 15-30 degree centigrade.<sup>10</sup> Misoprostol is a prostaglandin E<sup>1</sup> analogue, a methyl ester of prostaglandin E, additionally methylated at C-16.<sup>9</sup> It is used orally for the treatment of peptic ulcer. It is cheap, stored at room temperature and has shelf life of several years. It is a potent uterine stimulant when administered orally and vaginally in the induction of abortion, cervical ripening and induction of labour. It doesn't cause hypertension and is effectively absorbed from the mucosa following oral, vaginal and rectal administration.<sup>11</sup> It is also useful in the treatment of PPH unresponsive to oxytocin and ergometrine,<sup>12</sup> and its use has been suggested for the management of third stage of labour. Vaginal route is more effective than oral route and is associated with lesser degree of side effects in the induction of abortion.<sup>13</sup> Bioavailability of vaginal misoprostol is 3 times higher than that of orally

administered misoprostol.<sup>13</sup> Oral and sublingual misoprostol have quickest onset of action and high peak plasma concentration as compared to the vaginal route.<sup>14</sup> Vaginal route is not suitable in cases of PPH and for the management of third stage of labour as the drug is washed away before adequate absorption so rectal route has been advocated for the management of PPH as it has longer half life and thus prolongs uterine contraction which controls bleeding.<sup>13</sup> Oral misoprostol free acid is rapidly absorbed and is detected in circulation within 2 minutes of oral intake. Peak serum levels are achieved within 12 to 60 minutes and are high in oral as compared to the rectal route. Thus the oral route is potentially advantageous. Shivering and pyrexia are the main side effects of misoprostol.<sup>15</sup> Its other side effects are nausea, vomiting and diarrhoea.<sup>15</sup> Active management of third stage of labour is useful in preventing PPH.<sup>16</sup> Active management of third stage of labour with the use of conventional oxytocic agents is not practical in resource-poor settings as in developing countries because of the need for proper storage, protection from light, need for refrigeration, parenteral administration by skilled personnel and high cost. Use of Misoprostol as a uterotonic agent in the management of third stage of labour has been recommended by International Federation of Gynaecology and Obstetrics (FIGO) and International Confederation of Midwives (ICM), in situations where safe administration of injectable oxytocin and ergometrine is not feasible. Oral misoprostol because of its cost effectiveness, thermostability, easy administration by oral route, long shelf life without special storage conditions is a promising drug for such situations and the purpose of this study was to compare it against intramuscular oxytocin in the management of the third stage. The outcomes measured were duration of third stage, amount of blood loss and incidence of PPH, use of additional oxytocic drugs, drop in haemoglobin and haematocrit, need for blood transfusion, need for manual removal of placenta and occurrence of side effects such as shivering, fever, nausea, vomiting and diarrhoea.

### Patients and Methods

The quasi-experimental study was conducted in the department of Obstetrics and Gynaecology Unit II, Dow University of Health Sciences and Civil Hospital, Karachi, over a period of 6 months from June 20 to December 19, 2006.

A total number of 70 patients who were admitted through outpatient department (OPD) or were admitted in delivery suite with anticipated vaginal delivery were selected. Half of the patients were allocated to receive oral misoprostol 600µg (3tablets of 200µg) and 35 patients were allocated to receive 10 units intramuscular

oxytocin for the management of third stage of labour. The technique used for sampling was non-probability convenience sampling. The inclusion criteria for the study entailed: pregnant nulliparous and multiparous women, in active labour and expecting to have vaginal delivery. The exclusion criteria comprised history of previous caesarean section, history of asthma, deranged liver function in severe pregnancy-induced hypertension, and history of viral hepatitis. After informed consent, data was collected on a proforma containing information on maternal demographic characteristics such as age, weight, parity, gestational age at delivery, obstetrical history, including parity, history of PPH, essential or pregnancy-induced hypertension. Labour details were also recorded concerning induction, augmentation of labour, mode of delivery, episiotomy, vaginal or cervical tears. Haemoglobin and haematocrit was performed at the time of admission and repeated 24 hours after delivery. Delivery was conducted by resident R-1 or above. Third stage of labour was managed by early cord clamping and cutting, controlled cord traction and uterine massage. Blood loss was subjectively estimated by visual estimation of blood in a steel bedpan connected to the delivery table. Blood was collected with the help of a plastic sheet. Patients were observed in the labour room for side effects such as shivering, fever (temperature  $\geq 100^{\circ}\text{F}$ ), nausea, vomiting and diarrhoea and were followed in the ward upto a period of 24 hours after delivery. Data was analysed on SPSS version 10. Continuous variables such as age, parity, weight, gestational age, duration of third stage of labour, amount of blood loss, drop in haemoglobin and haematocrit were presented as mean  $\pm$  standard deviation. Independent sample t test was applied after checking for normal distribution, by Kolmogorov Smirnov test ( $p > 0.05$ ) to compare weight between the two groups. Similarly, independent sample t test was applied for drop in haematocrit and haemoglobin. Main outcome measures i.e duration of third stage (minutes) and amount of blood loss (ml) were checked for normal distribution by applying Kolmogorov smirnov test and were found non-normally distributed ( $p < 0.001$ ) so Mann Whitney U test was applied to compare these variables between Oxytocin and Misoprostol groups. Level of significance was  $\leq 0.05$  for all statistical tests.

Percentages were calculated for qualitative variables i.e mode of delivery, fever, shivering, nausea and vomiting, blood loss  $\geq 500\text{ml}$ , need for blood transfusion and additional oxytocic drugs. Chi square test was applied to compare shivering, augmented labour, episiotomy, and also collectively for all adverse effects and those labour

variables which could influence amount of blood loss i.e augmented labour, episiotomy, forceps delivery, vaginal and cervical tears. As the cell count was  $<5$  in certain qualitative outcome variables i.e blood loss  $>500\text{ml}$ , use of additional oxytocic drugs, blood transfusion, fever, nausea, vomiting, forceps, and vaginal/cervical tears, Fischer exact test was applied to compare these variables. Level of significance was taken as  $\leq 0.05$ .

## Results

A total of 70 women were enrolled in the study and were divided into 2 equal groups: 35 (50%) in the oxytocin group (Group 1); and 35 (50%) in the Misoprostol group (Group 2).

The commonest age group was 21-25 years in both the groups. Mean age of patients in group 1 was  $26.6 \pm 6.11$  years and  $25.26 \pm 4.93$  in group 2. Mean weight of patients in group 1 was  $60 \pm 8.09\text{kg}$  and  $61.42 \pm 7.03\text{kg}$  in group 2 ( $p=0.754$ ).

Mean gestational age (weeks) of patients in group 1 was  $37.97 \pm 1.74$  and that of group 2 was  $37.71 \pm 2.16$  ( $p=0.586$ ).

In group 1, 69 (98.57%) were delivered by spontaneous vaginal delivery and 1 (1.42%) by forceps delivery.

**Table-1:** Comparison of labour variables influencing amount of blood loss.

Variable	Group 1 (Oxytocin) (n= 35) n (%)	Group 2 (Misoprostol) (n= 35) n (%)	p value
◆ Augmented Labour**	06 (17.14)	04 (11.42)	0.495
◆ Forceps delivery	01(2.85)	0	1.000
◆ Episiotomy***	10(28.57)	17(48.57)	0.086
◆ Vaginal/cervical tear	1(2.85)	0	1.000

Values given in parentheses are percentages.

◆ Overall insignificant difference between variables influencing blood loss ( $p=0.630$ ).

\* Labour which progressed normally with adequate uterine contractions without the use of drugs till delivery.

\*\* Labour in which drug (Oxytocin infusion) was used to achieve adequate uterine contractions before delivery.

\*\*\* Incision given at perineum to increase the diameter of vulval outlet at delivery.

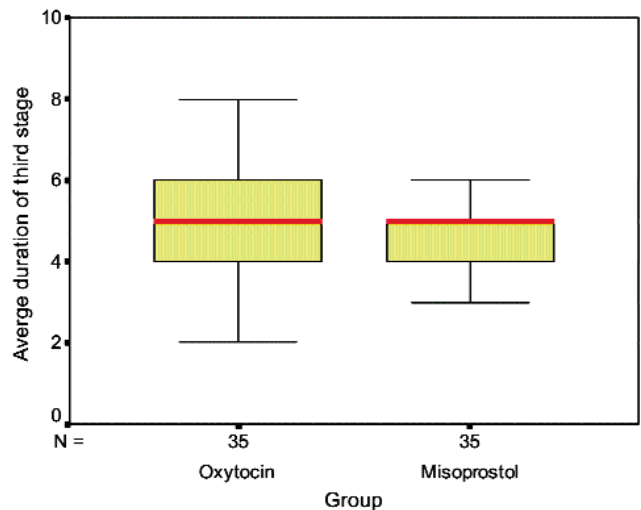
**Table-2:** Comparison of adverse effects between two groups n=70.

Adverse Effects	Group 1 (Oxytocin) (n= 35) n (%)	Group 2 (Misoprostol) (n= 35) n (%)	p value
Shivering	3(8.6)	11(31.4)	0.017
Fever *	0	6(17.1)	0.025
Nausea and Vomiting	1(2.85)	3(8.57)	0.614
Total	4	20	$<0.001$

Values given in parentheses are percentages.

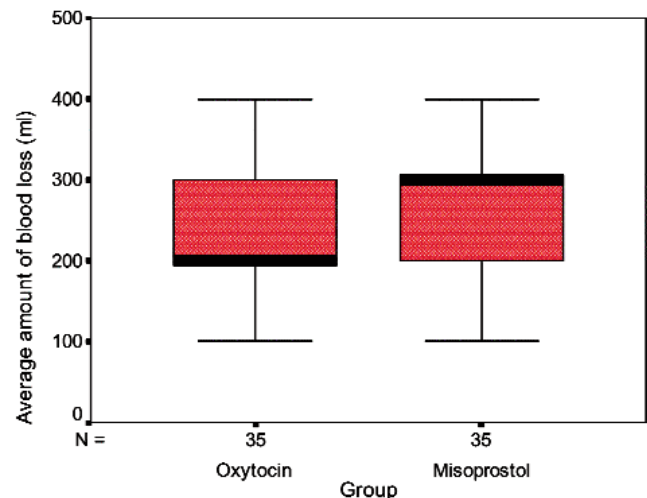
Overall Significant difference in adverse effects between two groups ( $\chi^2=16.23$ ,  $p=<0.001$ ).

\*Temperature  $\geq 100$ .



Insignificant difference between two managements ( $5.37 \pm 2.20$  vs.  $5.23 \pm 2.46$ ;

**Figure-1:** Comparison of duration of third stage of labour between two groups, n = 70.



Insignificant difference between two managements ( $267.14 \pm 140.35$  vs.  $302.86 \pm 160.4$ ;

**Figure-2:** Comparison of average blood loss between two groups n = 70.

Six (17.14%) patients needed augmentation with Syntocinon in group 1 as compared to 4 (11.42%) in group 2 (Table-1).

Average duration of third stage of labour in group 1 was  $5.37 \pm 2.20$  minutes and in group 2 it was  $5.23 \pm 2.46$  minutes ( $p=0.451$ ) (Figure-1).

Average amount of blood loss was higher in group 2 than group 1 ( $302.86 \pm 160.4$  vs  $267.14 \pm 140.35$ ;  $p=0.236$ ) (Figure-2). Amount of blood loss  $>500\text{ml}$  was found in

3(8.57%) patients in group 1 as compared to 4(11.42%) in group 2 ( $p>0.05$ ). Overall incidence of PPH defined as blood loss  $>500\text{ml}$  in all the study patients was 10% ( $n=7$ ). None of the patients in the study population had blood loss  $\geq 1000\text{ml}$ .

In group 1, 8.57% patients needed additional oxytocic drugs as compared to 11.42% in group 2 ( $p>0.05$ ). Blood transfusion was needed postpartum in 1(2.85%) patient in group 1 as compared to 2(5.71%) patients in study group 2 ( $p>0.05$ ). No patient required manual removal of placenta.

The average drop in haemoglobin concentration (g/dl) observed in group 1 was  $1.55\pm 0.38$  vs  $1.66\pm 0.61$  in group 2 ( $p=0.684$ ). Average drop in haematocrit (%) level though observed more in group 2 was insignificant between the two groups ( $4.18\pm 0.64$  vs  $4.50\pm 0.92$ ;  $p=0.133$ )

Adverse events of both drugs were the secondary outcome measures and were noted separately (Table-2).

## Discussion

The risk of maternal death due to PPH is approximately 1 in 1000 deliveries in the developing world.<sup>3</sup>

Caliskan E et al in a randomised controlled trial compared oral misoprostol  $400\mu\text{g}$  (followed by 2 doses of  $100\mu\text{g}$  4 hours apart) with intravenous infusion of oxytocin, combination of misoprostol and intravenous oxytocin infusion and combination of methylergonovine and intravenous oxytocin infusion. They also reported insignificant difference in the length of third stage of labour between misoprostol and intravenous oxytocin infusion groups.<sup>17</sup> Pharmacokinetic studies show that absorption times of intramuscular and intravenous oxytocin are similar (1-2min) so their effectiveness is also expected to be similar.<sup>18</sup>

Average amount of blood loss was higher in group 2 as compared to group 1 but it was not statistically significant. Overall incidence of PPH (defined as blood loss more than  $500\text{ml}$ ) in the study group was 10%. Incidence of PPH with blood loss  $>500\text{ml}$  but  $< 1000\text{ml}$  in group 2 was slightly higher than group 1 (11.42% vs 8.57%) but it was also not statistically significant. None of the patients in the study group had massive PPH defined as blood loss more than  $1000\text{ml}$ . World Health Organisation (WHO) multicentre randomised trial which compared  $600\mu\text{g}$  oral misoprostol with 10 IU of intramuscular or intravenous oxytocin showed that blood loss was consistently higher in group 2, with higher rates of blood loss more than  $1000\text{ml}$  as compared to group 1, Similarly misoprostol is also associated with increased use of additional oxytocics.<sup>18</sup>

Cochrane database review of 72 randomised controlled trials on use of misoprostol, by Gulmezuglu et al reported significantly more number of women with blood loss  $>1000\text{ml}$  who received oral misoprostol  $600\mu\text{g}$  as compared to conventional oxytocics.<sup>19</sup> Our finding of insignificant difference in the mean blood loss is not consistent with this but a larger sample size may make difference in result. Our result compares with that of a prospective randomised study by Zachariah ES et al in which they compared oral misoprostol  $400\mu\text{g}$ , intramuscular oxytocin and intravenous ergometrine for the management of third stage of labour. They also reported insignificant difference in the mean blood loss between the three groups.<sup>15</sup>

Our finding of no case with blood loss more than  $1000\text{ml}$  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  $1000\text{ml}$ .<sup>20</sup>

Mean duration of third stage with misoprostol was  $5.23\pm 2.46$  minutes in our study whereas another study on 600 women receiving same dose of misoprostol reported longer duration of  $7.9\pm 4.2$  minutes.<sup>21</sup> There were slightly greater percentage of patients in group 2 as compared to group 1 who required additional oxytocics in the same proportion as the increased percentage of patients with blood loss  $>500\text{ml}$ . But the largest ever trial on misoprostol use in third stage of labour involving  $>9000$  women demonstrated higher proportion of women requiring additional oxytocic drugs.<sup>18</sup>

Proportion of women requiring blood transfusion postpartum was slightly higher in misoprostol group, but it was not statistically significant.

Adverse effects such as shivering, fever defined as temperature  $>100^\circ\text{F}$ , were found in significantly higher proportion of patients in misoprostol group which is consistent with most of the studies on misoprostol.<sup>15,17</sup> The reported incidences of shivering in WHO multicentre trial was 41% with a dose of  $600\mu\text{g}$  and 37% with a dose of  $400\mu\text{g}$ .<sup>18</sup> El-Refaey et al have reported incidence of shivering as high as 62% with a dose of  $600\mu\text{g}$ .<sup>22</sup>

Nausea and vomiting like other prostaglandin related side effects, though higher in misoprostol group, failed to reach statistical significance. Our result of insignificant difference in nausea vomiting is consistent with that of El-Refaey in a prospective observational study who also reported nausea and vomiting in 8% of cases with Misoprostol.<sup>22</sup> Significantly high incidence of nausea, vomiting was also not reported in the WHO multicentre randomised trial.<sup>18</sup> Diarrhoea was not reported by any of

our patients. It is also not a frequently quoted side effect as is the case with shivering and pyrexia.

### Conclusion

Oral misoprostol is an almost equally effective uterotonic drug when compared with intramuscular oxytocin for the management of third stage of labour, but with higher side effects of fever and shivering. Thus it can be considered a reasonable alternative to oxytocin for the management of third stage of labour to prevent PPH, at places where parenteral drug administration and maintenance of required temperature for storage of oxytocin is not feasible.

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