

# A Randomized Comparison of Rectal Misoprostol with Syntometrine on Blood Loss in the Third Stage of Labour

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## ABSTRACT

**Objectives:** a) To compare the clinical effect of rectal misoprostol with intramuscular syntometrine in reducing blood loss in the third stage of labour; b) to determine the severity and incidence of side effects of both drugs and c) to measure blood loss, patient tolerance and acceptance of rectal misoprostol.

**Methods:** One hundred and forty parturients were randomly allocated to receive intramuscular syntometrine (syntocinon 10 IU + ergometrine 0.5 mg) or rectal misoprostol 400 µg within five minutes of the delivery of the anterior shoulder. Blood loss was measured by the use of a plastic collection drape. Additional oxytocic therapy was instituted for uterine atony or if blood loss was in excess of one litre.

**Results:** There was no significant difference in patient demographics of each treatment group (Table 1). There was no difference in mean duration of the third stage of labour ( $8.4 \pm 14$  min vs  $7.8 \pm 6.6$  min). The mean blood loss from those parturients receiving misoprostol ( $180.1 \pm 120$  mls) was not significantly different ( $p = 0.5$ ) from those receiving syntometrine ( $197 \pm 176.97$  mls) for the active management of the third stage of labour. Treatment with syntometrine was associated with a significant elevation of post-partum systolic blood pressure compared with misoprostol treatment (mean increase  $0.57 \pm 18.79$  mmHg vs  $-1.43 \pm 14.17$  mmHg, (mean  $\pm$  SD),  $p < 0.04$ ). Rectal misoprostol was well tolerated in 88.5% of participants, 11.4% reported that insertion was uncomfortable, of which 2.8% reported that they would have preferred parenteral drug administration.

**Conclusion:** The clinical effect of rectal misoprostol and intramuscular syntometrine were not different at the doses used in the active management of the third stage of labour in this study. Rectal misoprostol was well tolerated by the patients and had a low side effect profile. Blood loss assessment using the blood collection drape is of invaluable benefit in resource-poor settings.

## Comparación Randomizada del Misoprostol Rectal con la Sintometrina en la Pérdida de Sangre en la Tercera etapa del Parto

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## RESUMEN

**Objetivos:** a) Comparar el efecto clínico del misoprostol rectal con la sintometrina intramuscular en la reducción de la pérdida de sangre en la tercera etapa del parto, b) determinar la severidad y la incidencia de los efectos colaterales de ambos medicamentos, y c) medir la pérdida de sangre, la tolerancia de las pacientes y la aceptación del misoprostol rectal.

**Métodos:** Ciento cuarenta parturientas fueron elegidas de forma aleatoria para que recibieran la sintometrina intramuscular (syntocinon 10 IU + ergometrina 0.5 mg) o el misoprostol rectal 400 µg dentro de los cinco minutos de la salida del hombro anterior. Se midió la pérdida de sangre usando una bolsa plástica de recolección de sangre. Se instituyó una terapia oxitócica adicional para la atonía uterina o para el caso de que la pérdida de sangre excediera un litro.

**Resultados:** No hubo diferencia significativa en la demografía de los pacientes de cada grupo de tratamiento (tabla 1). No hubo diferencia en la duración promedio de la tercera etapa del parto ( $8.4 \pm 14$  min vs  $7.8 \pm 6.6$  min). La pérdida promedio de sangre de las parturientas que recibieron el miso-

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*prosto*l ( $180.1 \pm 120$  mls) no fue significativamente diferente ( $p = 0.5$ ) de las que recibieron *sintometrina* ( $197 \pm 176.97$  mls) para el tratamiento activo de la tercera etapa del parto. El tratamiento con *sintometrina* estuvo asociado con una elevación significativa de la presión sistólica postparto comparada con el tratamiento con *misoprostol* (aumento promedio  $0.57 \pm 18.79$  mmHg vs  $-1.43 \pm 14.17$  mmHg, (media  $\pm$  sd),  $p < 0.04$ ). El *misoprostol* rectal fue bien tolerado por el 88.5% de las participantes, 11.4% reportaron que la inserción fue incómoda, y de ellas 2.8% reportó que hubieran preferido una administración parenteral del medicamento.

**Conclusión:** El efecto clínico del *misoprostol* rectal y el de la *sintometrina* intramuscular, no fueron diferentes en las dosis usadas en el tratamiento activo de la tercera etapa del parto en este estudio. El *misoprostol* rectal fue bien tolerado por las pacientes y tuvo un perfil de efecto colateral bajo. La evaluación de la pérdida de sangre utilizando una bolsa de recolección de sangre posee un valor inapreciable en escenarios de recursos pobres.

West Indian Med J 2009; 58 (3): 202

## INTRODUCTION

Post-partum haemorrhage (PPH) accounts for approximately 28% of maternal deaths in developing countries (1), equivalent to 100 deaths per 100 000 deliveries (2); 13% of maternal deaths in the United States of America [USA] (3) and one death per 100 000 deliveries in Britain (2). In Jamaica, post-partum haemorrhage (PPH) accounted for 12 deaths per 100 000 deliveries in the triennia 1993–1995 (McCaw-Binns *et al*, personal communication, Jamaica). In addition, it is a significant contributor to maternal morbidity (3, 4).

At the University Hospital of the West Indies (UHWI), the active management of the third stage of labour protocol relies primarily on pharmacotherapy as prophylaxis against PPH. Meta-analysis of controlled trials suggests that oxytocics reduce post-partum haemorrhage rates from 10 per cent to 6 per cent (5). Despite the use of available drugs (oxytocin, syntometrine and methylergonovine maleate) in a timely fashion, significant haemorrhage continues to be a threat to maternal well-being (2).

Prostaglandins have proven value in the management of PPH even in cases not responding to syntometrine/oxytocin (6–8). However, the ideal route of administration and the optimal dose has not been established. Numerous studies advocating the off-label use of misoprostol (Cytotec; Searle AG, Chicago, IL) have shown varying efficacy based on the route of administration and dose used (9–13). The pharmacokinetics suggest that the median onset of action of oral misoprostol (6.0 min, range 4.0–10.0 min) is significantly more rapid than by the rectal route (11.0 min, range 7.0–13.0 min) resulting in earlier clinical efficacy (14). In practice, rectal misoprostol offers a longer duration of sustained uterine contractility even though its onset of action is slower.

Conventional oxytocics (syntometrine, oxytocin) are of little value in resource-poor countries where refrigeration is not readily available as they require storage at 2–8°C and are degraded by heat and light. In contrast, misoprostol is easily stored at room temperature, not degenerated by light or heat, is relatively inexpensive and has good transmucosal absorption (13) and relatively few side effects.

Other distinct advantages of the rectal route include its post-partum administration in patients with vomiting (which is not an uncommon intrapartum event) and in those unable to take medications due to anaesthesia. In addition, rectal misoprostol is associated with less systemic side-effects (14) and can be appropriately used in the domiciliary setting where parenteral access may not be an option.

We therefore sought to determine the clinical effect of rectal misoprostol compared with syntometrine in reducing blood loss in the third stage of labour at the UHWI, Jamaica.

## SUBJECTS AND METHODS

This prospective open randomized controlled trial was conducted on the labour ward at the UHWI, Jamaica, over a period of six months to compare the clinical effect of rectally administered misoprostol (400 µg) and syntometrine in the management of the third stage of labour, to determine the severity and incidence of side effects of both drugs and to establish patient tolerance and acceptance of rectally administered misoprostol. The study was approved by the Ethics Committee of the Faculty of Medical Sciences, University of the West Indies/University Hospital of the West Indies.

The participants were counselled and written informed consent obtained from one hundred and forty parturients. Exclusion criteria included previous post-partum haemorrhage, hypertensive disorders, previous Caesarean section, intrauterine death in current pregnancy, sepsis/pyrexia  $> 38^{\circ}\text{C}$ , antepartum haemorrhage, symptomatic anaemia or haemoglobin below 8 g/dL.

Computer generated block randomization was used to randomly assign participants to receive pharmacotherapy (syntometrine *versus* misoprostol) for the active management of the third stage of labour. Both the patient and the midwife conducting the delivery were aware of the drug administered.

The main outcome parameter was measured blood loss up to one hour post-delivery. Secondary outcome measures included the proportion of subjects with post-partum haemorrhage, the proportion of subjects who need additional utero-tonic agents and incidence of adverse events.

On arrival at the labour ward, a blood sample for haemoglobin and haematocrit was collected at insertion of an intravenous access. When vaginal delivery was imminent the parturient was assigned a study number generated by computer block randomization. The pharmacotherapeutic agent administered was based on the assigned number being either intravenous syntometrine or rectally administered misoprostol. The uterotonic agent was given within five minutes of delivery of the anterior shoulder by an *accoucheur* not involved in the delivery.

Additional therapeutic uterotonics were administered when there was clinical evidence of poor uterine tone post delivery or in the presence of uterine haemorrhage in excess of one litre (Table 2). Intravenous methylergonovine maleate 0.2 mg was given initially and if necessary a slow intravenous infusion of syntocinon 20 U in 500mls dextrose water was administered.

Blood loss was measured by use of a modified plastic collection drape which was placed beneath the parturient. The collection drape measured 168 cm x 84 cm, contained folded over side-wings and a 34-cm collection pouch (Figs. 1 – 4). The side wings acted as a chute for the collection of all



Fig. 1: Placement of the blood collection drape on delivery bed.



Fig. 2: Sterile drapes overlying collection drapes at delivery.



Fig. 3: Sterile drapes moved away to allow blood to be collected by plastic drape.



Fig. 4: Graduated measuring cylinder used for quantifying blood loss.

blood lost at the time of delivery into the collection pouch made by folding the distal end of the drape. The usual sterile drapes were placed above the blood collection drape. Prior to delivery of the fetus every effort was made to avoid soiling of the sterile drapes as these were not weighed. Post-delivery, the sterile drape overlying the collection drape was removed to facilitate the use of the collection drape. Post-partum blood loss was measured from the commencement of the third stage up to one hour following delivery.

One hour after delivery, side effects were evaluated by the use of a questionnaire that documented subjective and objective parameters – nausea, vomiting, diarrhoea, hot flushes, fever, shivering, headache and vertigo. Concomitantly, the post delivery temperature and blood pressure were recorded. These were compared with the intrapartum recordings just prior to delivery. The haemoglobin and haematocrit were measured on day one after delivery.

### Data analysis

Data analysis was conducted using STATA 7.0, College Station. The primary outcome measure in this study was the volume of postpartum haemorrhage. A sample size of 140 with 70 patients in each group was required to detect a difference in blood loss of 50 mls with a power of 90%. This was computed based on a previous study (11) which showed a variance for blood loss of 92 mls in the misoprostol group. An intention to treat analysis strategy was employed. Clinical and haematological parameters were compared using *t* and chi-square tests and repeated measures of analysis of variance (ANOVA) as appropriate. A *p* value < 0.05 was considered significant.

### RESULTS

All one hundred and forty participants completed the study, with 70 receiving rectal misoprostol and 70 receiving syntometrine. The clinical characteristics of the sample are seen in Table 1, which showed no difference in the variables measured between the two treatment groups. Similarly, comparison between groups by selected variables of labour (Table 2)

showed no statistically significant differences between treatment groups.

For the purpose of this paper, PPH was defined as blood loss in excess of 500 mls (WHO) at the time of delivery or a significant fall in haematocrit > 10% 24 hours post delivery. There was no statistical difference in the incidence of post-partum haemorrhage 3/70 (4.3%) in the group given syntometrine and 1/70 (1.4%) in those receiving misoprostol (risk ratio 1.5 with 95% CI 0.84, 2.75). Overall PPH occurred in 4/140 (2.85%) of participants. Severe PPH ≥ 1000 mls occurred in one participant, 1/140 (0.7%), who was given syntometrine with a measured blood loss of 1000 mls. There was an equal requirement for therapeutic oxytocics in 6/70 (8.6%) in both treatment groups. None of the patients in either treatment group required blood transfusion and there were no maternal deaths.

Shivering was significantly higher in those receiving misoprostol (16.4%) as compared to those receiving syntometrine (8.6%). There were no cases of severe shivering and in affected parturients most cases resolved within 10 to 30 minutes. Eighty-five per cent of parturients (20/23) in the

Table 1: Demographic characteristics of participants of the study

Demographic Characteristics	Syntometrine (1 ampoule)		Misoprostol (400 µg)		<i>p</i> Value
	Values	Range	Values	Range	
Maternal age *, years	27.4 ± 6.1	17 – 41	28 ± 5.9	16 – 42	NS
Parity#	0	0 – 4	1	0 – 8	NS
Gestational age *, week	39.1 ± 1.8	31.7 – 42.4	39.2 ± 1.2	32.4 – 42	NS

\* Data are presented as mean ± SD # Values are medians NS – not significant

Table 2: Variables of labour by treatment group

	Syntometrine (1 ampoule)	Misoprostol (400 µg)	<i>p</i> values
Measured post-partum blood loss up to one hour post delivery, mls	197 ± 177	180.1 ± 120	NS
Measured post-partum blood loss > 500 mls	(3)	(1)	NS
3 <sup>rd</sup> stage duration	8.4 ± 14 min	7.8 ± 6.6 min	NS
Spontaneous/Assisted labour	(69/1)	(67/3)	NS
Oxytocin used in 1 <sup>st</sup> and 2 <sup>nd</sup> stage	(32)	(33)	NS
Intravenous fluid used in labour, mls	752.1 ± 596.5	684 ± 613.3	NS
Additional oxytocin after initial methergin infusion, mean dosage, IU	15 ± 8.4	13.3 ± 10.3	NS
Perineal trauma: (epis/laceration)	(22)	(19)	NS
Manual removal of placenta	(1)	(0)	NS
Neonatal weight (kg)	3.3 ± 0.6	3.3 ± 0.4	NS

Data are presented as mean ± standard deviation (SD) or absolute counts (N), NS – not significant, epis = episiotomy

misoprostol group who experienced shivering reported that it would not be a deterrent factor in their future choice of uterotonic agent. None of the participants in this study received epidural anaesthesia which is a well-recognized cause of shivering.

Two participants in the study experienced tetanic uterine contractions causing severe lower abdominal pain one hour after rectal misoprostol insertion. Both cases were refractory to orally administered acetaminophen but responded to intramuscularly administered meperidine hydrochloride. The symptoms in the most adversely affected parturient persisted in excess of an hour. No tocolytic therapy was required to achieve relief from the pain.

Nausea was experienced by three parturients (2.1%) and vomiting by one parturient (0.7%) who received syntometrine. None of the parturients who received misoprostol reported such symptoms. There were no reports of pyrexia (temperature > 38°C) or diarrhoea following misoprostol therapy.

In this study, 12 parturients who received syntometrine had post-partum systolic blood pressure readings above 140 mmHg. There was a statistically significant increase in the post-partum systolic blood pressure in those receiving syntometrine compared with those receiving misoprostol (Table 3).

Table 3: Mean differences between antepartum and post-partum clinical characteristics by treatment group.

Variables	Syntometrine	Misoprostol	<i>p</i> values
Hb difference g/dL	0.56 ± 0.72	0.50 ± 0.77	NS
Hct difference %	1.95 ± 2.65	1.34 ± 3.17	NS
Temperature difference °F	-0.59 ± 1.15	-0.65 ± 1.17	NS
Systolic BP difference mmHg	-0.57 ± 18.79	1.43 ± 14.17	0.04
Diastolic BP difference mmHg	-1.72 ± 12.47	1.50 ± 11.74	NS

Mean difference = (antepartum mean – post-partum mean) ± SD

When participants were asked how well misoprostol was tolerated, only 8 (11.4%) reported that insertion was uncomfortable, of which 2 (2.8%) reported that they would have preferred parenteral drug administration. The remaining 62 participants were either unaware of rectal insertion [24] (34.3%) or reported no discomfort [38] (54.2%).

## DISCUSSION

In Jamaica, PPH is the third leading cause of maternal death (15) which remains largely preventable. Multivariate sensitivity analysis of the Kigoma study (Tanzania) and a Gambian study showed that rectal misoprostol (1000 µg) is effective in treating patients satisfying the criteria for post-partum haemorrhage (blood loss greater than 500 mls prior to administration of misoprostol) by preventing 1647 cases of severe PPH per 10 000 births (16). The findings of this study using a lower dose of misoprostol demonstrated that the clinical effect (post-partum blood loss) of rectal misoprostol

(400 µg) was similar to standard therapy for PPH prophylaxis, with minimal side effects and was well tolerated. These findings have been corroborated by several other studies (7, 11, 17).

A strength of this study is that it highlights the use of a blood collection drape for measuring blood loss at delivery. This may be of potential benefit in the domiciliary setting where blood loss is often underestimated (18). Blood within the placental interstices and loss due to splash, spillage or soiling of delivery drapes is often underestimated. The presence of amniotic fluid admixed with blood has been shown to contribute to overestimation. In the present study group, a placental dish was used to collect any liquor drained during the intrapartum period to avoid overestimation.

The major advantages of utilizing rectal misoprostol include its ease of administration, low side effect profile and its ability to be administered in patients experiencing vomiting during the intrapartum period; whereas oral misoprostol would have been ineffective. Chong *et al* have shown that doses of oral misoprostol above 400µg were associated with significant shivering and pyrexia (60%). Side effects are related to the peak plasma concentrations of misoprostol acid achieved and this is dependent on dose and route of administration (14). Khan *et al* showed that misoprostol acid was detected in the serum in both oral and rectally administered routes as early as 7.5 minutes but rectally the mean serum concentration and the peak plasma concentration were lower (20). However, the duration of action of rectal misoprostol was longer. As the minimal therapeutic plasma concentration of misoprostol acid remains unknown then PPH prophylaxis may be achieved at serum levels attainable by the rectal route and the higher levels attained orally may not necessarily lead to clinical superiority (20). These findings underscore the use of rectal misoprostol for PPH prophylaxis despite the findings of the World Health Organization multicentre randomized trial (21) which advocated the oral route based on pharmacokinetic studies.

The findings of this study corroborates with the meta-analysis of several others (22) in making the case for establishing a new standard protocol for the management of the third stage of labour using misoprostol.

## ACKNOWLEDGEMENTS

The study was funded by the Mona Campus and Research Publication Committee, The University of the West Indies. The author wishes to recognize the invaluable contribution of the postgraduate residents and nursing staff of the Labour Ward, University Hospital of the West Indies.

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