Oral misoprostol versus intramuscular oxytocin in the active management of the third stage of labour

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ABSTRACT

Introduction: Although the third stage of labour is usually uneventful, several significant complications may be encountered that may lead to maternal morbidity and mortality, especially primary postpartum haemorrhage. The objective of this study was to compare 400 µg oral misoprostol with 10 IU intramuscular oxytocin in the active management of the third stage of labour.

Methods: This was a prospective randomised controlled clinical trial in which 200 parturients at term who had vaginal delivery were randomly assigned into two groups: oral misoprostol and intramuscular oxytocin, after the delivery of the baby and the clamping of the umbilical cord. The primary outcome was the incidence of primary postpartum haemorrhage. Secondary outcomes included a drop in haemoglobin concentration 48 hours after delivery, the need for extra oxytocics, duration of the third stage of labour and side effects of the oxytocics. These results were subjected to statistical analysis using chi-square test or student's *t*-test.

Results: No occurrence of primary postpartum haemorrhage or significant difference in the drop in haemoglobin concentration levels was reported after delivery (p-value is 0.49), and no significant differences were observed in other secondary outcome measures with the exception of nausea, which occurred solely in the misoprostol group (4 percent, p-value is 0.04).

Conclusion: Oral misoprostol appeared to be as effective and as safe as intramuscular oxytocin in the active management of the third stage of labour.

Keywords: intramuscular oxytocin, oral misoprostol, third stage of labour

Singapore Med J 2010;51(3):207-211

INTRODUCTION

The period following the delivery of a baby is a time of relief and joy for all involved. It is a period when both the parturient and the accoucher may be relieved with the safe delivery of a healthy baby and hence be lured into a false sense of security that all is safe and well. However, potential danger lurks for the mother during this period.[1-5]

Although the third stage of labour is usually uneventful, several significant complications may be encountered that may lead to maternal morbidity and mortality.[1,2] The most common and the most fatal of these complications is primary postpartum haemorrhage (PPH).[1-3,6-9] Other complications may include genital tract laceration, retained placenta and uterine inversion.[10] Among the three stages of labour, mortality and morbidity mostly occur in the third stage of labour (as a result of PPH),[10] yet little thought or attention seems to be devoted to this stage of labour compared to the first and second stages.[11] Apart from maternal mortality, morbidities that may follow PPH include anaemia, prolonged hospital stay and difficulty in establishing breastfeeding.[11-15] A blood transfusion may alleviate the anaemia and shorten hospital stay, but it carries risks of blood transfusion reactions and infections, especially of viral infections such as human immunodeficiency virus (HIV) and hepatitis B.[2,5,12-15] Access to safe blood transfusion is not universal, and this is especially so in developing countries. Even then, PPH can sometimes strain the resources of the best blood bank.[7,12] The evidence that active management of the third stage of labour reduces the frequency of PPH has been established for the last 17 years.[1,16-19]

Several oxytocics (uterotonics) have been employed in the active management of the third stage of labour. Ergometrine is effective, but its use has been limited by its side effects. Recently, oxytocin has been preferred. However, its use as a uterotonic in the active management of the third stage of labour is fraught with problems of storage, fake and substandard drugs, and the need for staff

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Table I. Demographic characteristics and events in the labour of the parturients.

Variable	Intramuscular oxytocin, 10 IU (n = 100)	Oral misoprostol, 400 µg (n = 100)	p-value
Demographic (mean ± SD)			
Age (years)	27.5 ± 3.5	27.1 ± 3.4	1.00
Gestational age (weeks)	39.0 ± 1.1	39.1 ± 1.2	0.28
Parity	0.8 ± 0.7	0.7 ± 0.7	0.72
Height (cm)	158.0 ± 4.1	157.0 ± 4.4	0.31
Weight (kg)	61.9 ± 5.4	62.1 ± 5.2	0.81
Event in labour			
Analgesia – pethidine, no (%)	70 (70%)	72 (72%)	0.53
Mean duration of 1st stage of labour (min)	6.2	6.0	0.42
Mean duration of 2nd stage of labour (min)	30.2	30.6	0.85
Mean duration of 3rd stage of labour (min)	4.5	4.6	0.22
Labour augmentation with oxytocin, no (%)	12 (12%)	15 (15%)	0.63

training in order to be able to administer it. An alternative, equally potent and safe drug would be welcomed. Prostaglandins have also been effectively used, but they are expensive. All these agents also have shortcomings with respect to their modes of storage and administration. Lately, oral misoprostol (prostaglandin El analogue) has been introduced as a uterotonic for the active management of the third stage of labour. Misoprostol is administered orally, and hence does not require special training for its administration. It does not need special storage facilities and is heat stable, especially in hot tropical environments. A study is required in order to determine if oral misoprostol is as effective as intramuscular oxytocin in the active management of the third stage of labour. This study was carried out to determine the efficacy and safety of oral misoprostol in comparison to intramuscular oxytocin in the active management of the third stage of labour.

METHODS

The study was conducted in the Obstetrics Unit of the Obafemi Awolowo University Teaching Hospital, Ile-Ife, Nigeria. There are 2,500 deliveries per year at this hospital. Two hundred low-risk term pregnant women were involved in two arms of the study.

This was a prospective randomised clinical trial. On admission into the labour ward, eligible parturients in an active phase of labour were randomised into two groups, A and B, by blocked (restrictive) double blind randomisation using random table generated numbers. Parturients who were randomised into Group A were administered 400 ug of misoprotol (Beijing Zizhu Pharmaceutical Company Ltd, Beijing, China) orally with about 50 ml of water, after the delivery of the infant and clamping of the cord. The parturients in Group B were administered 10 IU of oxytocin (Shijiazhuang Pharmaceuticals Group Ouyi Pharma Co Ltd, Shijiazhuang, Hebei, China) intramuscularly, also after the delivery of the infant and clamping of the cord. The placenta was actively delivered following the first uterine contraction felt after the oxytocics had been administered by controlled cord traction in all cases. Demographic characteristics, including maternal age, parity, weight, height and gestational age, were recorded.

The primary outcome measure was the incidence of PPH. This is defined by the World Health Organization (WHO) as blood loss ≥ 500 ml after vaginal delivery.[5,6] The blood loss at delivery was assessed by the attending accoucher by collecting all blood lost during and after the delivery of the placenta into a large kidney dish. This was subsequently measured in a graduated measuring jar by the investigator or by a senior registrar in the labour ward when the investigator was not available. Secondary outcome measures evaluated included an objective assessment of blood loss by recording the haemoglobin concentrations before and 48 hours after delivery. The packed cell volume was determined in the labour ward side room laboratory, using capillary tubes; these values were then divided by three to obtain the equivalent haemoglobin concentrations. Side effects (such as nausea, vomiting, shivering and elevated temperature), the need for additional oxytocics and the duration of the third stage of labour were also evaluated.

The inclusion criteria were all parturients in the active phase of labour with no known risk factors for PPH. Exclusion criteria included all parturients undergoing caesarean section, those with haematocrit < 30%, preeclampsia/eclampsia, grandmultiparae (five deliveries or more), multiple pregnancies, coagulation disorders, induced labour and other medical disorders in pregnancy. Parturients who refused to participate in the study were also excluded. Approval for the study was obtained from the institution's ethics committee, and written consent was obtained from the parturients.

Table II. Comparison of changes in the haemoglobin levels and side effects in the study groups.

Variable	Intramuscular oxytocin, 10 IU (n = 100)	Oral misoprostol, 400 ug (n = 100)	p-value
Change in haemoglobin levels			
Blood loss > 500 ml	Nil	Nil	
Use of additional uterotonics	4 (mean 1.96)	3 (mean 1.97)	0.70
Average blood loss (ml)	155.60	153.20	0.77
Mean pre-delivery haemoglobin (g/dL)	11.1 ± 0.6	11.1 ± 0.6	0.82
Mean 48 hours post-delivery	10.7 ± 0.6	10.8 ± 0.6	0.41
Mean reduction in haemoglobin (g/dL)	0.4	0.3	0.49

To determine the sample size for each arm of this study, the following formula was used:

$$n = \frac{1}{(1-f)} \quad \frac{2(Za + Zb)^2 \times p(1-p)}{(P_0 - P_1)^2} \quad \text{where}$$

n = minimum sample size of each arm of the study group.

a = probability of making type I error.

b = probability of making type II error.

Za = level of significance of type I error probability; determined from a statistical table based on the value of the level of significance, a; for this study, a was set at 0.05. The 96% confidence interval (Za) = 1.96 for a two-tailed test (standard normal deviate).

Zb = this is type II error probability. It was determined from a statistical table based on the acceptance power of comparison between the two groups. For this study, a power of 80% (0.8) was used; therefore, Zb = 0.84 .

P_0 = the proportion of the participants in the control group (oxytocin group) who were expected to exhibit the primary outcome of interest (i.e. PPH); 50% (0.5) was used.

P_1 = the proportion of the participants in the treatment group (misoprotol group) who were expected to exhibit the primary outcome of interest (i.e. PPH); a difference of 20% between P_0 and P_1 was considered to be significant. Hence, P_1 = 30 or 70%.

1 – f = the statistical power of comparison.

f = the proportion of study subjects who were expected to leave the study for reasons other than the outcome under investigation. This was placed at 10% (0.1).

p = $(P_0 + P_1)/ 2$ = 40% = 0.4, or 60% = 0.6

Therefore, n (sample size of one arm of this study) was given as:

$$\frac{1}{(1-0.1)} \quad \frac{2 \times (1.96 + 0.84)^2 \times 0.4 \times 0.6}{(0.5 - 0.3)^2}$$

$$= \frac{1.1\ (15.68 \times 0.24)}{0.04} = 103.488$$

Therefore, for each arm of this study, an average of 100 parturients was required.

The data obtained was recorded in a computer and analysed using the Statistical Package for the Social Sciences version 11.0 (SPSS Inc, Chicago, IL, USA). Statistical significance was elicited using the chi-square test and student's *t*-test, where necessary.

RESULTS

This prospective study evaluated 200 women (100 parturients each in the two study groups). Table I shows five demographic variables of the parturients, including their mean age, parity, height, weight and period of gestation in weeks. No statistically significant differences were found in any of these five variables, indicating that baseline characteristics of the parturients remained similar in the two arms of the trial (p [Pearson's chi-square test] > 0.05; not significant). All the parturients had spontaneous onset of labour. 12% and 15% of the parturients in the oxytocin group and misoprostol group, respectively, had augmentation of labour. 70% and 72% of the parturients in the oxytocin and misoprostol groups, respectively, had intramuscular pethidine as analgesic in labour. Table II shows that there was no incidence of PPH (blood loss > 500 ml) in both groups. Among all the selected parturients, seven needed additional uterotonics, four (4%) in the oxytocin group and three (3%) in the misoprostol group. This was not statistically significant. The average blood loss was also comparable between the two groups, with a mean blood loss of 155.60 ml for the oxytocin group and 153.20 ml for the misoprostol group. Pre-delivery and 48 hours post-delivery haemoglobin concentration levels were also comparable in both groups, with 11.1 g/dL and 10.7 g/dL recorded for the oxytocin group and 11.1 g/dL and 10.8 g/dL recorded for the misopostol group. The average reduction in haemoglobin concentration levels for the two groups was 0.4 g/dL for each arm of the study.

Table III shows that 4% of the patients who received misoprostol had nausea, which was statistically significant. Shivering occurred in 2% of parturients in the oxytocin group and 4% in the misoprostol group.

Table III. Profile of side effects in the study group.

Variable	Intramuscular oxytocin, 10 IU (n = 100)		Oral misoprostol, 400 µg (n = 100)		p-value†
Symptom	No	Yes (%)	No	Yes (%)	
Nausea	100	nil	96	4	0.04*
Vomiting	100	nil	100	nil	
Shivering	98	2	96	4	0.13
Rise in temperature	100	0	100	0	

* denotes statistical significance.
† using Pearson's chi-square test.

This was not statistically significant. These were the only side effects recorded in this study. No complication in the third stage of labour, such as a retained placenta, uterine inversion or cord detachment, was recorded in this study.

DISCUSSION

The third stage of labour carries the highest risk of mortality and morbidity for the mother.[1-13] This has to do with the potential for PPH, which accounts for about a quarter of maternal deaths worldwide.[5,6] Although specific studies on PPH are scarce in Nigeria, the contribution of PPH to maternal mortality has been well documented in various institutional studies across the country.[5-7,13-20]

It has been established that prophylactic administration of oxytocic agents in the active management of the third stage of labour could significantly reduce the incidence of primary PPH from 18% to 5%. In addition, the time for administration of therapeutic oxytocic drugs is reduced from 15 minutes to five minutes.[21,22] This practice has become a standard of obstetric care, and misoprostol has emerged as a promising treatment alternative.[10-13]

This prospective randomised comparative clinical trial showed that orally administered misoprostol, with its rapid onset of action, is as effective as intramuscular oxytocin in minimising blood loss in the third stage of labour. No incidence of PPH (blood loss < 500 ml) was recorded in both groups. The average blood loss, drop in haemoglobin concentration levels and the need for additional uterotonics in the two arms of the study were not statistically significant. This is similar to the findings in previous studies.[10-17]

The average duration of the third stage of labour was 4.59 minutes and 4.53 minutes for the misoprostol and oxytocin group, respectively. This was also not statistically significant (p = 0.22). The findings also agree with those of several other studies comparing misoprostol with oxytocin.[18-25]

In this study, an analysis of the side effects of the two uterotonic agents revealed that nausea was mainly seen in the misoprostol group, and this was a statistically significant finding (p = 0.04), while the incidence of shivering was not statistically different (p = 0.13). This is in tandem with the results of other studies.[22,26-28] However, these undesirable side effects of misoprostol were found to be self-limiting, and shivering could be contained by simply covering the patient with blankets. The frequency of shivering decreased significantly between two and six hours, from 18% at one hour to 3% in a 2–6 hour period, and fell to almost zero 7–12 hours later.[27,28] Unlike in other reports, elevated temperature was not recorded in this study.[22-26] Both shivering and pyrexia occurring with misoprostol are thought to be due to the prostaglandin E effect on central thermoregulatory centres, and Lumbiganon et al have reported that although these symptoms may be of limited clinical concern, they can make the accoucher suspicious of infection or malaria, leading to unnecessary investigations and antibiotic or anti-malaria treatment.[28] The incidence of shivering was also found to be lower in this study, similar to other studies using this dose of misoprostol as compared to studies utilising a higher dosage.[28,29]

Misoprostol has many advantages. It is cheap (320 Naïra [local currency] per treatment compared to oxytocin at 640 Naïra), has a long shelf life and is thermostable (storable at tropical temperatures, and hence requiring no refrigeration). No special training is needed to administer it, and it has an acceptable safety profile.

In conclusion, this study suggested that oral misoprostol appeared to be as effective and as safe in minimising blood loss in the third stage of labour as intramuscular oxytocin. Further research to determine the least effective dose of misoprostol that will result in the least acceptable side effects is recommended. Meta-analytic studies on this topic are also desirable. Misoprostol has great potential for use in the active management of the third stage of labour, especially in developing countries. Although this clinical trial was limited to low-risk parturients, misoprostol is also

effective in high-risk patients with bronchial asthma, pregnancy-induced hypertension and Rhesus-negative blood groups, where other oxytocics (especially ergometrine) may be contraindicated.

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