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Comparative Study in Efficacy between 600 Mcg Oral Misoprostol and 10 Units Oxytocin IM in Active Management of Third Stage of Labour

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Abstract

Aims: *This study was conducted with the aim of comparing the efficacy of oral misoprostol 600 mcg with intramuscular oxytocin 10 IU in the active management of third stage of labour.*

Methods: *This prospective comparative study was performed at Department of Obstetrics and Gynaecology, South Eastern Railways, Kolkata, a tertiary care hospital offering referral services to pregnant women.*

The aimed at to compare the efficacy of oral misoprostol with intramuscular oxytocin in the third stage of labour to prevent of postpartum hemorrhage. 60 women without risk of PPH were randomly allocated to receive either 600 mcg misoprostol orally (Group I) or 10 unit of oxytocin intramuscularly (Group II) within 1 minute of delivery. The efficacy and the safety of these two drugs were analyzed on the basis of percentages fall in hemoglobin (Hb) and hematocrit (Hct) level from before delivery to 8 completed hours after delivery, need for additional uterotonic agents, need for exploration and uterine evacuation, need for blood transfusion, duration of third stage of labour and the numbers of retained placenta and need for MRP.

Results: *Oral misoprostol was observed to be equally effective as intramuscular oxytocin in prevention of post-partum hemorrhage (PPH). There was no statistical difference in the duration of third stage of labour, need for additional uterotonics, need for uterine exploration/evacuation and need for blood transfusion in the two groups.*

Conclusions: *Routine use of oral misoprostol 600 mcg appears to be as effective as 10 IU intramuscular oxytocin in minimizing blood loss during the third stage of labour.*

Keywords: *misoprostol; active management of third stage of labour; side effects; oxytocin; blood loss; PPH.*

INTRODUCTION

WHO Recommendations for Active Management of the Third Stage of Labour (AMTSL), 2012 suggests use of uterotonics for the prevention of postpartum haemorrhage (PPH) during the third stage of labour for all births. Oxytocin (10 IU, IV/IM) is the recommended uterotonic drug for the prevention of PPH. However, injectable uterotonics are seldom available for births outside the health system. [1]

In low-income countries, PPH is a major cause of maternal death and arguably the most preventable. Attempts to reduce deaths from postpartum haemorrhage have been complicated by the fact that many deaths occur in out-of-hospital settings or too quickly for the patient to be transferred to a

health facility. For these reasons, the use of misoprostol to prevent or treat postpartum haem-orrhage has attracted considerable attention. [2]

Misoprostol, an inexpensive and stable prostaglandin E1 analogue, has been shown to stimulate uterine contractility in early pregnancy and at term. Administered orally or vaginally, it is effective for inducing abortion and labour, though it poses certain risks. Although originally introduced as a therapy for gastric ulcers, misoprostol is now widely used in reproductive health. For some indications it is now the optimal choice, whilst for others it provides an important alternative, especially in low-resource settings. The optimal dose varies widely from 20 to 600 mcg depending on the indication and gestation. Use of the correct dose is important, too low a dose will be ineffective and over-dosage can be dangerous for mother and baby. [3]

In a recent placebo-controlled trial in rural India in which babies were delivered by auxiliary nurse midwives at home or in village sub-centres, a significant reduction in postpartum haemorrhage and other complications was obtained with uterotonics without other components of the active management of the third stage of labour – umbilical cord clamping and controlled cord traction. [4]

Uterotonics act directly on the smooth muscle of the uterus and increase the tone, rate, and strength of rhythmic contractions. The body produces a natural uterotonic - the hormone oxytocin that acts to stimulate uterine contractions at the start of labour and throughout the birth process.

Drugs such as oxytocin, ergometrine, and misoprostol have strong uterotonic properties and are used to treat uterine atony and reduce the amount of blood lost after childbirth. Oxytocin is widely used for induction and augmentation of labour. The use of uterotonic drugs immediately after the delivery of the newborn is one of the most important actions used to prevent PPH.

WHO has developed guidelines supporting the use of a uterotonic when the full package of active management of the third stage of labour is not practised, which can be either oxytocin, 10 iu administered parenterally, or misoprostol, 600 mcg administered orally. [5]

Globally, misoprostol which first came into use for prevention of peptic ulcer disease and it was found useful for termination of pregnancy also and then as a miracle drug in the prevention of PPH. But the drug which is being used for the prevention of PPH universally is oxytocin for almost half a decade after being introduced in 1963 at the National Maternity Hospital in Dublin, Ireland.[1] Active management of third stage of labour (AMTSL) means expediting the process by early cord clamping, administration of a uterotonic, delivery of placenta by controlled cord traction following uterine contraction and finally uterine massage after delivery of the complete placenta.[2] Through this, shortening of third stage of labour by 50% and reduction of blood loss by 20% have been evidenced. Thus AMTSL has been now adopted globally as a strategy to reduce excessive blood loss during childbirth.[3]

The use of oxytocin in the AMTSL is having problems of storage, fake and substandard drugs, and the need for trained staff in order to administer it. Misoprostol on the other hand offers several advantages over oxytocin including a shelf life of several years, stability at high temperature, oral administration, minimal side effects, and also that it can be administered to hypertensive patients.[4]

MATERIALS AND METHODS

MATERIALS

Study area: Patients were selected mainly from population of Kolkata and adjacent area.

Study population: Patients from areas mentioned above admitted in the Department of Obstetrics and Gynaecology, Eastern Railways, Kolkata, a tertiary care hospital offering referral services to pregnant women.

Sample Size and Statistical Analysis: Statistical Software

Sample size had been calculated with help of Epi Info (TM) 3.5.3. EPI INFO which is a trademark of the Centers for Disease Control and Prevention (CDC).

Sample Size: The study was a cross sectional in which prospective comparative observation were performed. As per the study by Tuncer RA et al in developing countries, PPH continues to be a leading cause accounting for 43% of maternal deaths.

The number of subjects required for this study was 59.783 ~ 60 with power 81% (Proportion of maternal deaths due to PPH was 43% i.e. p= 0.43 as per the study by Tuncer RA et al). The formula used for sample size calculation was as follows:-

$$n = 4pq/ (L^2)$$

Where

n= Required sample size

p= 0.43 as the study per Tuncer RA et al

q = 1 - p

L = Loss %

Therefore, it is required to study 30 cases in one arm and 30 in another arm in the ratio 1:1.

Sampling Techniques: Patients were selected randomly with the help of computer generated random numbers.

Sample design: All the cases admitted in the Maternity ward in the Department of Obstetrics and Gynaecology, Eastern Railways, Kolkata, unless exclusion criteria met by random sampling.

RESEARCH HYPOTHESIS

Whether both oral misoprostol with intramuscular oxytocin are equally effective in the active management of third stage of labour?

AIMS AND OBJECTIVES

1. To compare the visually estimated blood loss in the third stage of labour of the two intervention groups.
2. To compare the average blood loss in the third stage of labour of the two intervention groups.
3. To compare the change in level of hemoglobin and hematocrit after comparing these in both pre-delivery and post-delivery of the two intervention groups.
4. To compare additional uterotonics used in the two intervention groups.
5. To compare the side effects of the two intervention groups.

Study design:

Comparative Observational Study

Criterion for case selection:

INCLUSION CRITERIA: Women who provide written and informed consent will be enrolled for the study provided they meet the below criteria :

- singleton pregnancy
- between 37 and 42 weeks of gestation
- anticipated vaginal delivery
- vertical lie
- no high risk factors

EXCLUSION CRITERIA: Patients with history of medical disorders like asthma, epilepsy, heart or renal disease will be excluded along with following conditions as well:

- haemoglobin <8 gm%
- pregnancy induced hypertension
- abruption placentae
- marginal placenta previa/low lying placenta
- multiple pregnancy
- grandmultipara
- malpresentation
- polyhydramnios
- previous uterine scar
- prolonged labour
- intrauterine fetal death
- coagulation abnormalities

METHODS

Active management of third stage of labour was done in Group A with misoprostol 600 mcg orally (n=30) and Group B with 10 units Oxytocin IM (n=30) after the delivery of the baby.

PARAMETERS AND PROCEDURES

STUDY TOOLS & TECHNIQUES: Out of the randomly selected 60 pregnant women active management of third stage of labour was done in Group A with misoprostol 600 mcg orally (n=30) and Group B with 10 units Oxytocin IM (n=30) after the delivery of the baby. Patients of the two groups of the study were also selected through Simple Random Sampling without replacement to avoid the selection bias.

Following criteria were observed during the study for both groups:

- Pulse rate and BP both before and after the third stage of labour.
- Duration of the third stage of labour (in min)
- The amount of blood loss (in ml) using calibrated plastic blood collection container or drape. Blood were collected after drainage of liquor and delivery of baby and were continued till the completion of third stage of labour
- Fall in Haemoglobin (Hb) level by comparing the Hb level during admission and after 24 hours of delivery
- Whether blood transfusion was required. If yes, then how many cases in each group.
- Whether any other Oxytocics were required or not

LABORATORY INVESTIGATIONS:

Investigations were performed for the following parameters as part of the study to reach a conclusion:

- Hb% in both groups before and after deliver
- Hematocrit
- PCV

RESULTS AND ANALYSIS

Statistical Analysis

Statistical Analysis was performed with help of Epi Info (TM) 3.5.3. EPI INFO is a trademark of the Centers for Disease Control and Prevention (CDC). Using this software, basic cross-tabulation, inferences and associations were performed.

χ^2 test was used to test the association of different study variables with the study groups. Z-test (Standard Normal Deviate) was used to test the significant difference between two proportions. t-test was used to compare the means. $p < 0.05$ was considered statistically significant.

Table-1: Comparison of base parameters of the patients of the two groups

p-value	t-test (t_{58})	Oxytocin (n=30)	Misoprostal (n=30)	Parameters (Mean±s.d.)
0.58	0.54	25.03±3.95	24.48±3.53	Age Group (in years)
0.29	1.06	24.58±0.68	24.32±1.07	BMI (in kg/m^2)
0.89	0.13	38.89±1.38	38.84±1.31	Period of gestation (in weeks)
0.64	0.46	5.11±0.32	5.07±0.26	Duration of third stage labour (in minutes)

There were no significant differences in the base parameters of the patients of the two groups ($p>0.05$). Thus the patients of the two groups were matched for their base parameters.

Table-2: Distribution of amount of blood loss of the patients

Oxytocin (n=30)	Misoprostal (n=30)	Amount of blood loss (in ml)
259.62±34.61	262.59±36.28	Mean±s.d.
260	260	Median
210 - 350	200 - 350	Range

The mean amount of blood loss (mean± s.d.) of the patients treated with misoprostal was 262.59±36.28 ml with range 200 - 350 ml and the median was 260 ml.

The mean amount of blood loss (mean± s.d.) of the patients treated with oxytocin was 259.62±34.61 ml with range 210 - 350 ml and the median was 260 ml.

Though the mean amount of blood loss of the patients treated with misoprostal was higher than that of the patients treated with oxytocin, t-test showed that there was no significant difference between the two means (t_{58}=0.30;p=0.76).

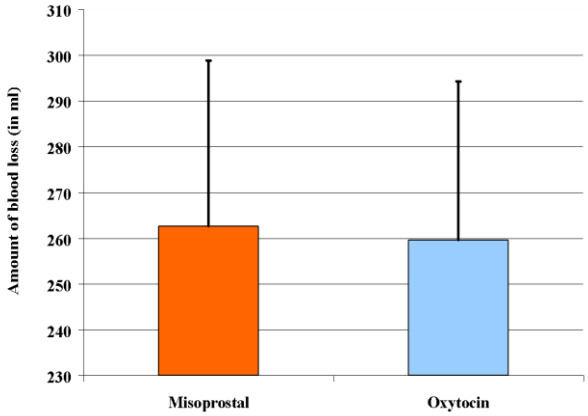


Table-3: Distribution of patients according to level of haemoglobin

p-value	t-test (t_{58})	Oxytocin (n=30)	Misoprostal (n=30)	Level of hemoglobin (in g/dL)
Pre-delivery				
0.24 NS	1.18	11.70±0.47	11.55±0.46	Mean±s.d.
		11.6	11.4	Median
		11.0 - 12.7	11.1 – 12.6	Range
Post-delivery				
0.42 NS	0.80	10.86±0.35	10.77±0.46	Mean±s.d.
		10.8	10.7	Median
		10.5 – 11.8	10.0 – 11.8	Range
Change				
0.47 NS	0.72	0.84±0.32	0.78±0.29	Mean±s.d.
		0.8	0.8	Median
		0.4 – 1.7	0.3 - 1.6	Range

* - Statistically Significant
NS- Not Significant

t-test showed there was no significant difference in pre-delivery level of hemoglobin of the two groups (t_{58}=1.18;p=0.24). However, post-delivery level of hemoglobin of the patients treated with misoprostal was lower than that of the patients treated with oxytocin (t_{58}=0.80;p=0.42) but it was not significant. But there was no significant difference in change in hemoglobin of the two groups (t_{58}=0.72;p=0.47).

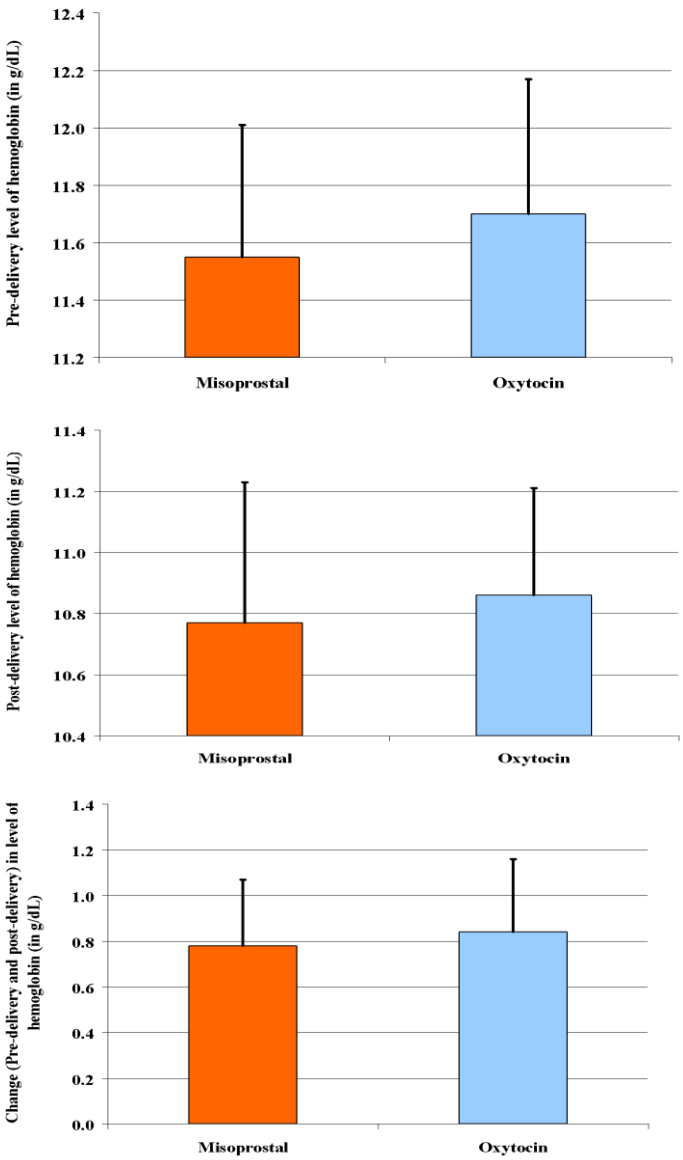
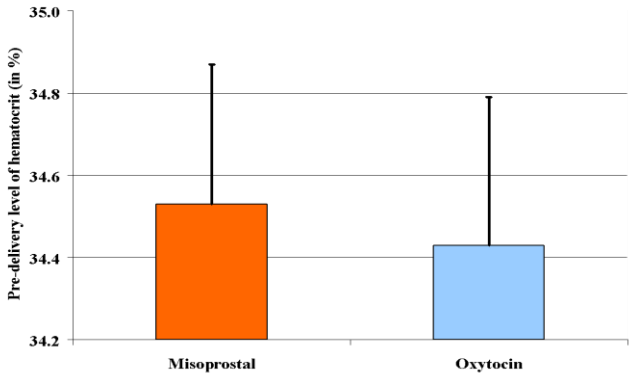


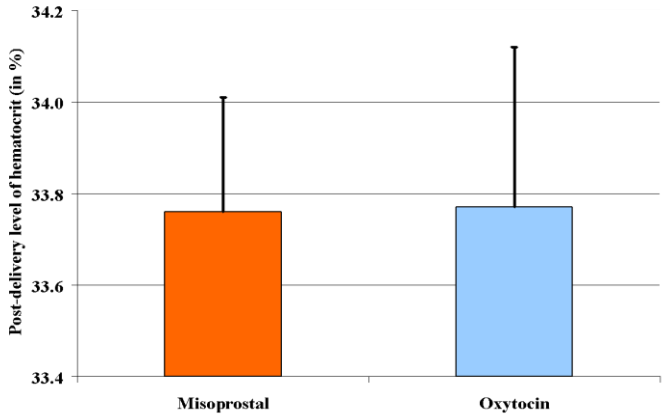
Table-4: Distribution of patients according to level of hematocrit (%)

p-value	t-test (t_{58})	Oxytocin (n=30)	Misoprostal (n=30)	Level of hematocrit (%)
				Pre-delivery
0.30 NS	1.04	34.43±0.36	34.53±0.34	Mean±s.d.
		34.4	34.5	Median
		33.7-35.2	33.6-35.1	Range
Post-delivery				
0.90 NS	0.12	33.77±0.35	33.76±0.25	Mean±s.d.
		33.7	33.8	Median
		33.2-35.0	33.2-34.2	Range
Change				
0.98 NS	0.02	0.66±0.22	0.76±0.21	Mean±s.d.
		0.7	0.8	Median
		0.2-1.0	0.3-1.2	Range

NS- Not Significant

t-test showed there was no significant difference in pre-delivery level of hematocrit of the two groups (t_{58}=1.04;p=0.30). However, post-delivery level of hematocrit of the patients treated with misoprostal was lower than that of the patients treated with oxytocin (t_{58}=0.12;p=0.90) but it was not significant. But there was no significant difference in change in hematocrit of the two groups (t_{58}=0.02;p=0.98).





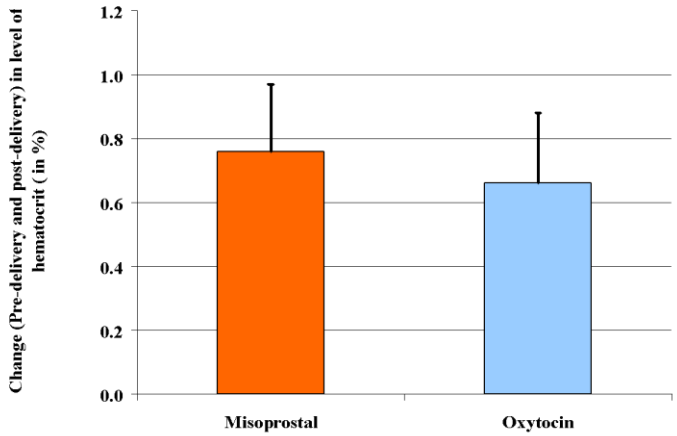


Table-5: Distribution of side effects of the patients

p-value	Z-test	Oxytocin (n=30)	Misoprostal (n=30)	Side effects
0.0524 NS	1.94	0(0.0%)	1(3.3%)	Fever
<0.001*	3.99	0(0.0%)	4(13.3%)	Shivering
0.0524 NS	1.94	0(0.0%)	1(3.3%)	Fever+Shivering

* - Statistically Significant

Test of proportion showed that proportion of patients with shivering who were treated with misoporstal (13.3%) was significantly higher than that of the patients treated with oxytocin (0.0%) (Z=3.99;p<0.001).

But though the proportion of patients with fever and fever & shivering who were treated with misoporstal (3.3%) was higher than that of the patients treated with oxytocin (0.0%), no significant difference was found among them (Z=1.94;p=0.05).

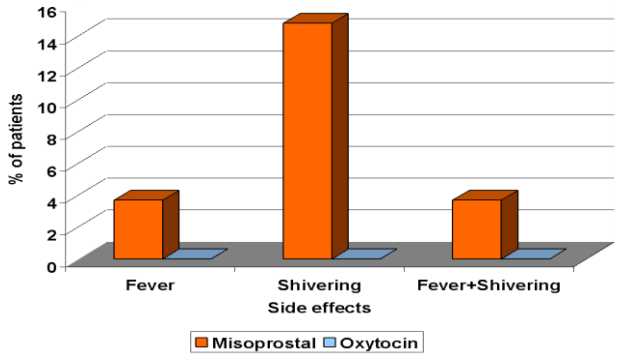
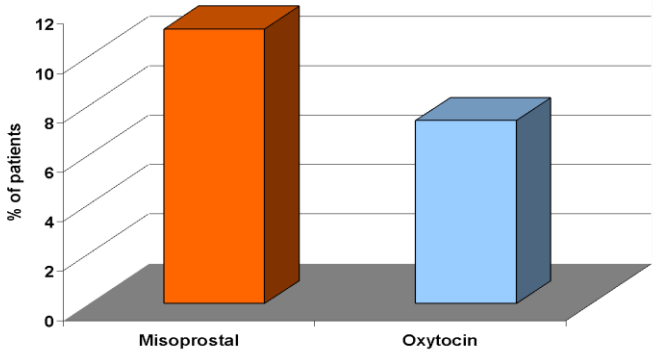


Table-6: Distribution of Additional Oxytocics of the patients

p-value	Z-test	Oxytocin (n=30)	Misoprostal (n=30)	Additional Oxytocics
0.34 NS	0.90	2(6.7%)	3(10.0%)	Yes

Test of proportion showed that proportion of patients with additional oxytocics who were treated with misoporstal (10.0%) was higher than that of the patients treated with oxytocin (6.7%) (Z=0.90;p=) but it was not significant.



DISCUSSION

Misoprostol in AMTSL has been reported to effectively reduce the incidence of primary PPH from 18% to 5%. In addition, the time for administration of therapeutic drugs is reduced from 15 minutes to five minutes. This practice has become a standard of obstetric care, and misoprostol has emerged as a promising treatment alternative. In this study, 600 mcg oral misoprostol was compared with 10 unit IM oxytocin for AMTSL and this dose of misoprostol is recommended by WHO for AMTSL when standard oxytocin is not available. This study found that there was no statistical significance between the effectiveness of these drugs in AMTSL and same result was shown which concluded that oral misoprostol 600 mcg can replace 10 unit intramuscular oxytocin in reducing postpartum hemorrhage in low-risk women, in developing countries. Several other routes of misoprostol like sublingual, vaginal, rectal and buccal have been compared and different doses ranging from 400 to 1000 mcg have been tried in AMTSL.

The number of patients in each group was 30 to make the groups comparable with the integer proportion of patients in the groups as 1:1. In other studies conducted in other places also the proportion of patients was as 1:1.

t-test showed that there was no significant difference between the mean age, mean BMI, mean period of gestation and mean duration of third stage labour of the two groups of the two groups ($p>0.05$). Thus the patients of the two groups were matched for all the base parametrs.

Thus as per other studies the two groups were balanced at randomization for potential confounding factors like age, BMI, and gestational age at delivery. The two groups were also comparable with regard to baseline prognostic labour characteristics like duration of third stage labour.

In this study the mean duration of third stage labour (mean± s.d.) of the patients treated with misoprostal was 5.07±0.26 minutes with range 5.0-6.0 minutes and the median was 5.0 minutes. The mean duration of third stage labour (mean± s.d.) of the patients treated with oxytocin was 5.11±0.32 minutes with range 5.0-6.0 minutes and the median was 5.0 minutes. Also t-test showed that there was no significant difference between the mean duration of third stage labour of the two groups ($t_{58}=0.46;p=0.64$).

As per study by Kaudel et al in the misoprostol group, mean duration of third stage of labour was 4.76 ±1.69 minutes whereas it was 4.39±1.37 minutes in the oxytocin group without any statistical significance (p-0.935) and similar result was obtained in three other comparative studies. The present study supported that the duration of third stage of labor is reduced by using uterotonics hence reducing the amount of blood loss.

The mean amount of blood loss (mean± s.d.) of the patients treated with misoprostal was 262.59±36.28 ml with range 200 - 350 ml and the median was 260 ml. The mean amount of blood loss (mean± s.d.) of the patients treated with oxytocin was 259.62±34.61 ml with range 210 - 350 ml and the median was 260 ml. Though the mean amount of blood loss of the patients treated with misoprostal was higher than that of the patients treated with oxytocin, t-test showed that there was no significant difference between the two means ($t_{58}=0.30;p=0.76$).

The amount of blood loss was statistically similar in both groups. The mean blood loss in the misoprostol group was 115.5 ±39.5 ml and in oxytocin group, it was 118 ± 48.6 ml, which was less than the blood loss in other studies.

This might be due to visual estimation of blood loss in the index study whereas other studies have used objective measurement of blood loss by placing drape under the buttocks before delivery and removing it after 1 hour postpartum. Most of the studies were unable to find the statistical significance in the blood loss while comparing these drugs in AMTSL.

3(10.0%) patients in misoprostol group and 2 (6.7%) patients in oxytocin group had blood loss more than 300 ml which was the maximum blood

loss estimated visually but visual estimation generally underestimates blood loss by 30%, which is clinically inadequate and has presented practical problem.

t-test showed there was no significant difference in pre-delivery level of hemoglobin of the two groups (t_{58}=1.18;p=0.24). However, post-delivery level of hemoglobin of the patients treated with misoprostal was lower than that of the patients treated with oxytocin (t_{58}=0.80;p=0.42) but it was not significant. But there was no significant difference in change in hemoglobin of the two groups (t_{58}=0.72;p=0.47). Similar trend had been observed in other studies.

Several other studies had also observed that peripartum fall in hematocrit level by at least 10% from before delivery to 24 hours after delivery, is a better definition than the volume criteria of PPH.

In this study the efficacy of the two regimes in the active management of the third stage of labour was mainly based on assessment of the degree of fall in hematocrit following delivery in the two groups.

t-test showed there was no significant difference in pre-delivery mean level of hematocrit of the two groups (t_{58}=1.04;p=0.30). There was no significant difference between post-delivery mean level of hematocrit of the patients treated with misoprostal and that of the patients treated with oxytocin (t_{58}=0.12;p=0.90). Also no significance difference was found for mean change in the level of hematocrit of the patients of the two groups (t_{52}=0.02;p=0.98).

These observations show that oral misoprostol and intramuscular oxytocin are more or less equally efficacious for AMTSL and this finding is consistent with data from another similar comparative study.

Test of proportion showed that proportion of patients with additional oxytocics or uterotonics who were treated with misoporstal (10.0%) was higher than that of the patients treated with oxytocin (6.7%) (Z=0.90;p=0.54) but it was not significant.

A similar comparative study done had shown less use of additional uterotonics in the misoprostol group as compared in the oxytocin group (7.1% vs 9.3%) , probably because of use of higher dose of misoprostol (800 mcg) in that study as compared to the index study but the result was insignificant.

Next additional parameter in assessment of efficacy of the two regimes was the need for blood transfusion following delivery and the need for exploration and uterine evacuation following delivery in the two groups. Fortunately no women required blood transfusion or uterine exploration/evacuation in these groups as they were well booked and had high hemoglobin and hematocrit before delivery. A similar comparative study done in India in 2011 showed that 1.9% of women in misoprostol and 1.1% of women in oxytocin required blood transfusion whereas MRP was needed in less than 1% in both the cases without bearing any significance.[24] As lesser number of women had participated in the index study, this might be the cause for no requirement of blood transfusion and MRP.

Test of proportion showed that proportion of patients with shivering within 1 hour postpartum who were treated with misoporstal (13.3%) was significantly higher than that of the patients treated with oxytocin (0.0%) (Z=3.99;p<0.001). But though the proportion of patients with fever and shivering with fever (max temp 100□F) who were treated with misoporstal (3.3%) was higher than that of the patients treated with oxytocin (0.0%), no significant difference was found among them (Z=1.94;p=0.05).

Regarding the side effects of oral misoprostol and intramuscular oxytocin, there were no serious side effects in this study. All the adverse effects were mild and they subsided spontaneously and none of the women required any medications for these effects.

In this study, the analysis of side effects of the two uterotonics revealed the presence of side-effects only in misoprostol group.

CONCLUSION

1. Misoprostol (oral 600 mcg) and oxytocin (IM 10 unit) were equally effective in AMTSL in this comparative study as there was no PPH in both the groups.
2. Oxytocin had lesser blood loss than Misoprostol but this was not statistically significant.
3. Oxytocin had the additional advantage of no side effects bearing statistical significance.
4. Hence, misoprostol which is as effective as oxytocin can be adopted for the active management of third stage of labour, with minimal self-limiting side effects.

RECOMMENDATION

This study revealed that Misoprostol (oral 600 mcg) and oxytocin (IM 10 unit) were equally effective in AMTSL as there was no PPH in both the groups. Also in Oxytocin group the patients had lesser blood loss than that of the patients of Misoprostol group ($p>0.05$). Oxytocin had the additional advantage of no side effects as compared to misoprostol. Hence, misoprostol which is as effective as oxytocin can be adopted for the active management of third stage of labour, with minimal self-limiting side effects.