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A COMPARATIVE RANDOMIZED CONTROLLED TRIAL OF MISOPROSTOL *PER RECTAL AND MISOPROSTOL PER ORAL* IN THE ACTIVE MANAGEMENT OF THIRD STAGE OF LABOUR

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ABSTRACT

Background : Postpartum haemorrhage, which is still one of the commonest causes of maternal mortality in the developing countries has been largely reduced in the developed countries by active management of third stage of labour (AMTSL).

Aim : To compare the efficacy and safety of Misoprostol 600 mcg *per rectal* with Misoprostol 600 mcg *per oral* in the active management of third stage of labour (AMTSL)

Materials and methods : a total of seventy patients of 34 to 42 weeks of gestation delivering vaginally satisfying inclusion and exclusion criteria in St. Martha's Hospital were selected for the study. They were randomly allocated into two groups. Group A included 35 patients and were given Tab Misoprostol 600 mcg *per oral*, Group B included 35 patients and were given Tab Misoprostol 600 mcg *per rectal* as a part of AMTSL.

Results : In the oral misoprostol group mean duration of third stage of labour was 5 minutes and 32 seconds, mean blood loss was 180.14ml and mean haemoglobin difference was 0.35 g/dl whereas in the rectal misoprostol group mean duration was 4 minutes and 50 seconds, mean blood loss was 120.43ml and mean haemoglobin difference was 0.24g/dl. All these observations were **statistically significant ($P < 0.05$).** In the study totally 4 patients had PPH, 3 in oral misoprostol group and 1 patient in rectal misoprostol group and is **not significant statistically ($P > 0.05$)**. All were managed with additional oxytocics. Side effects were more in the oral misoprostol group compared to rectal misoprostol group.

Conclusion : Misoprostol can be used effectively in the AMTSL for the prevention of PPH through different routes especially in non-institutional deliveries and in places of low resource settings. The mean duration of third stage of labour, the mean blood loss and the incidence of PPH are significantly less if Misoprostol is used through rectal route compared to the oral route. Side effects which is a major concern with oral misoprostol, can be significantly brought down if misoprostol is administered through rectal route.

KEYWORDS : Misoprostol, Active management of third stage of labour (AMTSL), Postpartum haemorrhage (PPH)

INTRODUCTION

One of the commonest causes of maternal mortality in the developing world is obstetric haemorrhage, particularly postpartum haemorrhage (PPH)[1], which is responsible for 25% of maternal deaths globally and also severe acute maternal morbidity including anemia, pituitary necrosis, shock, hysterectomy, loss of fertility etc. According to the recent Confidential Enquiries into maternal and Child health (CEMACH) Report, obstetric haemorrhage occurs in around 3.7 per 1000 births[2]. The incidence of fatal PPH has been largely reduced in the developed countries, largely because of active management of third stage of labour (AMTSL)[1] which when practiced routinely, can reduce haemorrhage by up to 60 %[3]. Routine use of AMTSL which includes the administration of uterotonic drug immediately after the birth of the baby, controlled cord traction and uterine massage, for all vaginal singleton births in health facilities is recommended by the International Federation of Gynecologists and Obstetricians (FIGO) and the International Confederation of Midwives (ICM), as well as by World Health Organization (WHO)[12].

The standard uterotonic agent used in the AMTSL is oxytocin. Among the uterotonics, oxytocin and methyl ergometrine are unstable when exposed to light and high ambient temperature. As these drugs are injectibles, they require qualified persons to administer the drugs. They also require readily available supply of sterile syringes and needles that must be handled and disposed properly. Even today a large number of deliveries occur with or without trained birth attendants in rural India where refrigeration and cold chain facilities are not available all the times. Hence these drugs lose their potency. Many birth attendants are not trained in giving parenteral injections[4].

Misoprostol, a methyl ester of natural prostaglandin E 1, was developed to treat NSAIDs induced peptic ulcer disease. Later on it gained popularity as an effective modality for cervical ripening. There are numerous advantages with regard to the use of misoprostol as it is inexpensive, stable at room temperature, easy to store and can be administered through various routes[5].

To reduce maternal mortality, the prophylactic use of misoprostol started gaining widespread and universal acceptance right after 2003 Italy conference for the active management of third stage of labour[5].

Government of India has included Tab Misoprostol 600mcg for Prevention of PPH & in training of active management of third stage of labor after delivery of baby for Auxiliary Nurse Midwives & staff nurses. WHO and Drug Controller General of India have also included Tab misoprostol for prevention & treatment of PPH in the list of essential drugs. Several studies are available worldwide on use of misoprostol as effective drug for prevention & treatment of PPH in different dosage form & routes. The drug Tab Misoprostol 600mcg is permitted & approved by Drug Controller General of India under rules 122-B of Drugs & Cosmetic Rule 1945 with effect from 14th Jan 2009 for the indication of prevention & treatment of PPH[4].

With the changing trends in modern practice, it is important that there is a set protocol for the use of uterotonic drugs depending on the patient's requirements, keeping cost effectiveness in mind and ensuring minimal side effects. Even though misoprostol is not a replacement for parenteral oxytocin, the study is undertaken as misoprostol is very useful in AMTSL especially in non-institutional deliveries and in places of low resource settings.

MATERIALS AND METHODS

Study was undertaken in the Department of Obstetrics and Gynaecology in St. Martha's Hospital, Bengaluru, for a period of 1 year from June 2015 to May 2016. Seventy pregnant women delivering vaginally with parity ranging from 0 – 4 and gestational age between 34 to 42 weeks selected for the study. Pregnant women with previous caesarean section, mal-presentation, severe anaemia, operative vaginal delivery, antepartum haemorrhage, multiple pregnancy, polyhydramnios, grand multiparity, pregnancy with glaucoma, asthma, cardiac disease, hypertension, diabetes mellitus were excluded from the study. Seventy patients satisfying inclusion and exclusion criteria were included in the study and they were randomly allocated into two groups on the basis of confidential allocation list prepared earlier. Written informed consent was taken and confidentiality maintained. Hospital ethical committee clearance was taken. Group A included 35 patients and were given Tab Misoprostol 600 mcg *per oral* and Group B included 35 patients and were given Tab Misoprostol 600 mcg *per* rectal immediately after the delivery of the baby.

Sample size was calculated based on the mean and standard deviation of a similar study conducted in Department of OBG in Mahatma Gandhi Medical College and Research Institute, Puducherry from Nov

2010 to May 2012[6] using the following formula

$$n = \frac{2\left(Z\frac{\alpha}{2} + Z\beta\right)^2 \sigma^2}{d^2} = \frac{2\,(1.96+0.84)^2\,70.65^2}{(205.94-156.6)^2} = 32$$

n= number of patients
α= type 1 error=0.05
β= power of study=0.80
d= difference in the means (difference in mean blood loss in both the groups in the study)

After admission, detailed history was taken and patient was examined. Patients were either allowed to progress spontaneously or induced if indicated. After the delivery of the baby, patients were randomly allocated into 2 groups. Parameters measured and compared in both the groups were – duration of third stage of labour, amount of blood loss (estimated by calibrated plastic blood collection drape in which blood was collected after drainage of liquor and delivery of baby), pre and post-delivery Hb% (Hb% was done at the time of admission and 24 hours post-partum), number of cases of PPH and side effects of drugs (such as fever, shivering, abdominal pain, diarrhea, nausea and vomiting). PPH patients in both the groups were manages with additional oxytocics.

STATISTICAL METHOD

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters and Student t test (two tailed, dependent) has been used to find the significance of study parameters on continuous scale within each group. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups. The difference among the groups was considered to be significant at $P < 0.05$.

OBSERVATIONS AND RESULTS

The purpose of the study is to find out which route of administration of Tab Misoprostol 600 mcg (*per oral* or *per rectal*) is better in view of amount of blood loss, duration of 3rd stage of labor and side effects and also to find out whether Tab Misoprostol 600mcg is suitable to be used as preventive measure for PPH in routine management of 3rd stage of labor especially in rural settings. Among the seventy patients enrolled in the study, 35 patients received tab misoprostol 600 mcg per oral and 35 patients received tab misoprostol 600 mcg per rectal as a part of active management of third stage of labour according to the random allocation list.

Mean age, parity, socioeconomic status and period of gestation were comparable in both the groups (Table 1).

Table 1 – distribution of patients according to the socio demographic pattern

Factors	Group A	Group B
Age (years)		
<20	2(5.7%)	2(5.7%)
20 – 30	28(80%)	23(65.7%)
31 – 40	5(14.3%)	10(28.6%)
Socioeconomic class		
Higher middle	1(2.9%)	3(8.6%)
Lower middle	30(85.7%)	26(74.3%)
Lower class	4(11.4%)	6(17.1%)
Parity		
Primigravida	14(40%)	11(31.4%)
Multigravida	21(60%)	24(68.6%)

The mean duration of third stage of labour was 5 minutes and 32 seconds in oral misoprostol group and 4 minutes and 50 seconds in the rectal misoprostol group. The difference was **statistically significant** ($P < 0.05$). The mean blood loss in the oral misoprostol group was 180.14 ml and in the rectal misoprostol group the mean blood loss was 120.43 ml and **it is statistically significant.** The mean haemoglobin difference (pre delivery and 24 hours post-delivery) was 0.35 g/dl and 0.24 g/dl in the oral and rectal misoprostol group respectively and **it is statistically significant.** (Table 2)

Table 2 – outcome of the study

	Group A	Group B	P value
Mean duration of third stage of labour	5 min 32 sec	4 min 50 sec	0.000307
Mean amount of blood loss	180.14 ml	120.43 ml	0.034
Mean amount of hemoglobin difference	0.35 g/dl	0.24 g/dl	<0.05

In the study, three patients in the oral misoprostol group had PPH and only one patient in the rectal misoprostol had PPH, which is **not significant statistically** ($P > 0.05$). (Table 3) All the patients who had PPH in both the groups were managed medically with additional oxytocics and none of them required surgical management.

Table 3 – number of PPH cases and the need for additional oxytocics

	Group A	Group B	P value
Number of PPH cases	3	1	0.614
Need for additional oxytocics	3	1	

Side effects like fever, shivering, abdominal pain, diarrhea, nausea and vomiting were more in the oral misoprostol group compared to rectal misoprostol group (Table 4).

Table 4 - distribution of cases according to the side effects

Side effects	Group A (n=35)	Group B (n=35)	Total (n=70)	P value
Shivering	14(40%)	4(11.43%)	18(25.71%)	0.00634
Pyrexia	4(11.43%)	1(2.86%)	5(7.14%)	0.16452
Abdominal Pain	10(28.57%)	3(8.57%)	13(18.57%)	0.03156
Diarrhoea	5(14.29%)	2(5.71%)	7(10%)	0.23014
Nausea	5(14.29%)	1(2.86%)	6(8.57%)	0.0876
Vomiting	3(8.57%)	1(2.86%)	4(5.71%)	0.30302

DISCUSSION

The active management of the third stage of labor is traditionally performed with the routine use of intravenous oxytocin. To substitute for oxytocin and to prevent postpartum haemorrhage misoprostol was chosen because it has similar advantages but with minimal side effects, low shelf life, inexpensive and easily available. It is easy to use, does not require special storage conditions, is thermostable and has a shelf life of several years. These advantages make it a useful drug in reducing the incidence of postpartum hemorrhage in developing countries.

In the present study the age of the patients ranged between 18 and 39 years and maximum number of patients in both the groups were in the age group of 20 – 30 years (80 % of the patients in Group A and 65.71 % of the patients in Group B were in the age group of 20 – 30 years) which is in accordance with other studies conducted by Prata N and others on misoprostol and active management of third stage of labour[7] in which the mean age was 25 years and by Masoumeh Mirtemouri on the efficacy of rectal misoprostol for the prevention of PPH[8]

In both the groups most of the patients were multigravidae, 60% in oral misoprostol group and 68.57% in rectal misoprostol group.

In the present study, the mean duration of third stage of labour in the oral misoprostol group was 5 minutes and 32 seconds and in the rectal misoprostol group was 4 minutes and 50 seconds and this difference is statistically significant. This is in accordance to a Comparative Study of Oral, Rectal Misoprostol with Intravenous Methylergometrine in Active Management of Third Stage of Labour conducted by Samal R, Coumary SA, John LJ, Ghose S. where mean duration of third stage of labour in rectal misoprostol group was 3.69 ± 0.72 min and in oral misoprostol group was 6.66 ± 1.08 min which was statistically significant[6].

In the present study, the mean blood loss in the oral misoprostol group was 180.43 ml and in the rectal misoprostol group the mean blood loss was 119 ml. This is in accordance to a study conducted by Mansouri and Alsahly on oral and rectal misoprostol in active management of third stage of labour, where women in oral misoprostol group lost significantly more blood than the women who had rectal administration 232.8 ml vs. 207.2 ml respectively[9].

The mean amount of fall in haemoglobin level were more in oral misoprostol group compared to rectal misoprostol group and the results were statistically significant which is in accordance with a study conducted by Kaudel and others in Tribhuvan University teaching hospital[10] and Shresta and others on Rectal Misoprostol versus Intramuscular Oxytocin for Prevention of Pospartum Hemorrhage[11]. Totally there were 4 cases of PPH in the study, 3 patients in the oral misoprostol group and 1 patient in the rectal misoprostol group which was statistically not significant. All patients who had PPH were managed medically and none of them required surgery which is in accordance with studies conducted by Mukta Mani[3] and Shresta[11]. Side effects like fever, shivering, abdominal pain, diarrhea, nausea and vomiting were more in the oral misoprostol group compared to rectal misoprostol group. Similar results were also noted in other studies conducted by Dr Mehta Amulya Udayan[4] and Mukta Mani[3].

CONCLUSION

Misoprostol can be used effectively in the active management of third stage of labour for the prevention of PPH through different routes. The mean duration of third stage of labour, the mean blood loss in the third stage of labour and the incidence of PPH are significantly less if Misoprostol is used through rectal route compared to the oral route. Side effects which is a major concern with misoprostol, can be significantly brought down if misoprostol is administered through rectal route. Misoprostol - which is affordable, stable at room temperature, can be easily administered through different routes, can be effectively administered *per rectal* for the active management of third stage of labour as an alternative to standard uterotonic oxytocin, especially in low resource settings.

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