ORIGINAL STUDY

Oral Misoprostol: A Safe and Effective Alternative in Comparison to Conventional Uterotonic Agents in the Active Management of Third Stage of Labor

[1]Mahmud Ghazala, [2]Tasnim Nasira, [3]Fatima Saba

[1]Head, Maternal and Child Health Center, Pakistan Institute of Medical Sciences, Islamabad, Pakistan

[2]Associate Professor, Maternal and Child Health Center, Pakistan Institute of Medical Sciences, Islamabad, Pakistan

[3]Postgraduate Resident FCPS, Unit-1, Maternal and Child Health Center, Pakistan Institute of Medical Sciences, Islamabad Pakistan

Correspondence: Mahmud Ghazala, Head, Maternal and Child Health Center, Pakistan Institute of Medical Sciences, Islamabad Pakistan, Phone: 051-9261273, Fax: 051-9263488, e-mail: helloghazala@hotmail.com

Abstract

Objective: To determine the efficacy and safety of oral misoprostol with intravenous oxytocin and syntometrine in the active management of third stage of labor.

Methodology: 325 women were randomly allocated by convenient sampling to receive either 10 IU of intravenous oxytocin or 10 IU of oxytocin with 0.2 mg of Methergine (syntometrine) or 400 mcg of oral misoprostol at the delivery of anterior shoulder. Main outcome measures were estimation of blood loss > 500 ml, drop in hemoglobin/hematocrit levels and adverse effects of drugs.

Results: Estimated blood loss was significantly higher in group misoprostol group (p = 0.016) but comparable to oxytocin group (p = 0.40). Drop in hemoglobin level was comparable in all the three groups (p = 0.106). Drop in hematocrit value was significant for misoprostol and syntometrine (p = 0.022) but comparable to oxytocin. Nausea and vomiting was common in oxytocin and syntometrine group whereas fever and shivering was the leading adverse effect in misoprostol group.

Conclusion: Misoprostol is an effective and safe alternative to intravenous uterotonic agents in the active management of third stage of labor both at tertiary and community level.

Keywords: Oxytocin, misoprostol, third stage of labor.

INTRODUCTION

Postpartum hemorrhage is an important cause of maternal morbidity and mortality especially in the developing countries.[1] Postpartum hemorrhage, the loss of more than 500 ml of blood after delivery occurs in upto 18% of births.[2] The primary cause of PPH is uterine atony which accounts for 70% of cases leading to severe postnatal anemia and hemorrhagic shock requiring blood transfusions and major surgical interventions.[3,4]

The best preventive strategy is the active management of third stage (AMTSL) of labor which involves administering a uterotonic drug with or soon after delivery of the anterior shoulder, controlled cord traction and fundal massage.[5-7] When compared to expectant management, AMTSL decreases the incidence of PPH by 68%.[5]

Most of the uterotonics require parenteral administration and maintenance of cold chain which is necessary for their efficacy, is not always possible in some hospitals or rural communities due to nonavailability of sterile needles, syringes or refrigerating equipment.[8] Misoprostol a prostaglandin E1 analogue first introduced as an anti-inflammatory drug for peptic ulcer disease. Later on it gained popularity as an effective modality for medical evacuation of uterus in spontaneous miscarriages, therapeutic termination of first and second trimester pregnancies, cervical ripening agent and for induction of labor,[4] is an orally active uterotonic agent when administered allows the uterus to contract within few minutes.[9] It is stable at room temperature, inexpensive and rapidly absorbed into the circulation after oral administration.[1]

The purpose of the study was to compare the efficacy and safety of oral misoprostol in the active management of third stage of labor with the currently used intravenous syntocinon and syntometrine and to see if oral misoprostol could be used in home deliveries in rural communities.

MATERIALS AND METHODS

A randomized controlled trial was conducted from 1st Jan to 31st Dec 2006 at Maternal and Child Health Center, Pakistan

Institute of Medical Sciences, Islamabad. A total of 325 women in their reproductive age groups between 19-36 years having singleton pregnancy and low-risk for vaginal delivery were included in the study.

Exclusion criteria: Women with chorioamnionitis, preterm labor, history of postpartum hemorrhage, polyhydramnios, and lower segment ceserean delivery in previous pregnancies were excluded from the study. All the conditions which were a contraindication to use of prostaglandin and uterotonic agents like severe pre-eclampsia, HELLP syndrome, asthma or hypersensitivity reaction were excluded.

Written consent was taken from the woman at time of admission and purpose of study was explained. Women were randomly allocated to receive either intravenous 10 IU of oxytocin or 10 IU oxytocin with 0.2 mg Methergine (syntometrine) or 400 mcg of oral misoprostol (2 tablets) at the delivery of anterior shoulder. Randomization was not carried out until vaginal delivery was imminent.

Hemoglobin and hematocrit values were measured at the time of admission to labor ward. At the time of delivery of anterior shoulder, either intravenous oxytocin or syntometrine was administered or 400 mcg of oral misoprostol was given with a sip of water. Signs of placental separation (lengthening of cord, gush of blood and straightening of uterine fundus) were noted and placenta was delivered by controlled cord traction. An additional oxytoxic agent was administered (oxytocin or syntometrine) if the uterus failed to contract after one minute of delivery of placenta or there was an excessive vaginal bleeding inspite of administration of initial uterotonic agents. After delivery, a sterile preweighed drape or pad was given to the woman for the next one hour. All the soaked drapes and pads were weighed on a weighing scale which was then subtracted from the initial weight of dry pads. A 100 gram increase in weight was considered to be equivalent to 100 ml of blood loss (assuming specific gravity of blood equivalent to 1gm/ml). This gave us the estimated blood loss in milliliters. The woman was kept under observation, encouraged to breast feed the baby. Strict record of her vitals was kept and bleeding per vaginum and uterine contractility were noted every 15 minutes for the first hour and every 30 minutes for the next hour. Any heavy bleeding was recorded within 24 hours of delivery. Hemoglobin and hematocrit values were carried out within 24-48 hours of delivery. Since 500 ml of blood loss signifies a drop of 1gm of hemoglobin, so in our study the difference in pre and post-delivery hemoglobin was estimated to calculate the blood loss in milliliters. Side effects of these uterotonic agents were noted i.e, nausea, vomiting, headache, fever and shivering.

Outcome measures: The primary outcome measures were the amount of blood loss during delivery and the occurrence of postpartum hemorrhage defined as, blood loss > 500 ml, determined by documenting vital signs and observing bleeding per vaginum. Safety of the drugs was assessed by drugs adverse effects like nausea, vomiting, shivering, fever which were inquired and noted one hour postdelivery.

Statistical analysis: Data was analyzed using SPSS v15. Descriptive statistics was used to calculate mean and standard deviation for quantitative variables and frequencies with percentages for qualitative variables. Chi-square and Kandall's Taub tests were used to compare nominal and ordinal variables respectively. One way ANOVA test with Tukey' Post Hoc test was used to compare means in three drug groups. Level of significance was set at 5%.

RESULTS

During our study period of one year, 325 patients were eligible for randomization by convenient sampling. Out of the study population of 110 (33.8%) women received oral misoprostol, 110(33.5%) received oxytocin and 105(32.3%) received syntometrine for the active management of third stage of labor (Flow chart 1). None of the women withdrew from the study. The demographic characteristics like age of woman, gestational age and parity were comparable in all the three drug groups (p = 0.363, 0.573, 0.907 respectively) (Table 1). The estimated blood loss by pre and postweighed pads was significantly less in the syntometrine group when compared to misoprostol group (270 ml *vs* 300 ml; p = 0.016), but was comparable in misoprostol and oxytocin group (300 ml *vs* 287 ml; p = 0.40).

The drop in hemoglobin levels was comparable in all the three groups (p = 0.106) (Table 2). The analysis showed that there was a significant drop in hematocrit value in all the three drug groups (p = 0.022), though the further analysis on the basis of individual drugs revealed that misoprostol group was associated with significantly more hematocrit drop in comparison

Table 1: Demographic characteristics

Variables	*Misoprostol(n=52)*	*Oxytocin(n=53)*	*Syntometrine(n=55)*	*P-value*
Age(years) Mean(SD)	25.75 ± 4.47	25.19 ± 4.33	26.04 ± 4.53	0.363
Gestational age(weeks) Mean(SD)	39.04 ± 1.56	39.04 ± 0.15	39.11 ± 0.16	0.573
Parity n(%) – Primigravida	53(16.3)	60(18.4)	52(16)	0.937
– Multigravida	57(17.5)	50(15.38)	53(16.3)	

Flow chart 1: Randomization of women

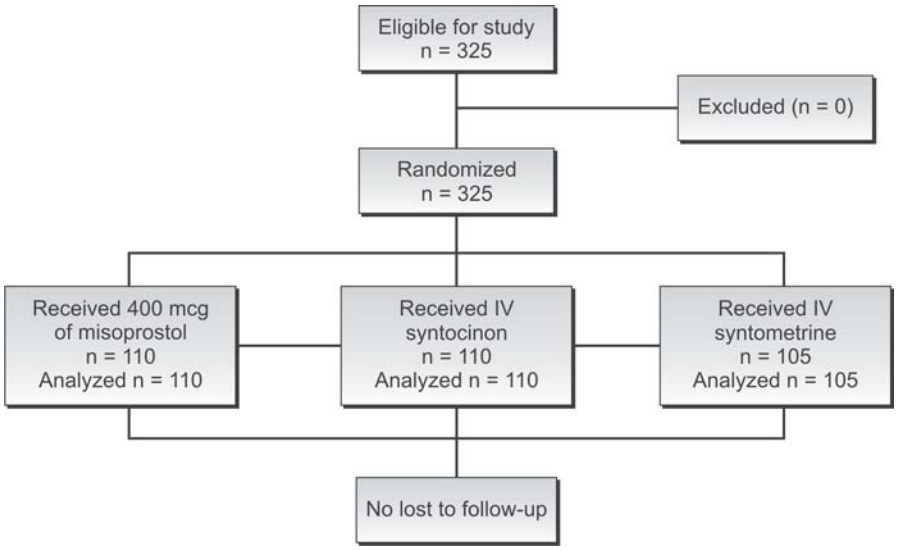

Table 2: Comparison of pre- and postdelivery hemoglobin (Hb)

Groups	*Predelivery Hb[a](g/dl)*	*Postdelivery Hb[b](g/dl)*	*Mean difference[b](g/dl)*	*p-value*
Oral misoprostol	10.85 ± 1.09	10.1 ± 1.09	0.68	
IV syntocinin	10.67 ± 0.99	10.0 ± 1.04	0.65	0.106
IV syntometrine	10.68 ± 1.03	10.07 ± 1.00	0.60	

[a]Hb = Mean(SD)
[b]Mean difference = Predelivery Hb – Postdelivery Hb

Table 3: Comparison of pre- and postdelivery hematocrit (Hct)

Groups	*Predelivery Hct[a]*	*Postdelivery Hct[b]*	*Mean difference*	*p-value*
Oral misoprostol	33.22 ± 2.96	32.50 ± 2.94	0.67*	0.022
IV syntocinin	32.52 ± 2.72	31.88 ± 2.74	0.64	
IV syntometrine	32.42 ± 2.68	31.83 ± 2.69	0.58*	

[a]Hct= Mean(SD)
[b]Mean difference = Predelivery Hct- postdelivery Hct
*Significant at 5% level

to syntometrine group but the drop in hematocrit was comparable to oxytocin (Table 3).

Blood loss >500 ml when assessed by pre and postweighed pads and by drop in hemoglobin level was comparable in all three drug groups (p = 0.83 *vs* 0.77 respectively) (Table 4).

As far as administration of additional uterotonic agents for the management of postpartum hemorrhage were concerned, none of the groups required statistically significant administration (misoprostol 1.5% *vs* oxytocin 1.5% *vs* syntometrine 1.2%; p = 0.954). It was observed that nausea and vomiting was commonly observed in oxytocin and syntometrine group (p-0.00) whereas more patients complained of shivering and fever in misoprostol group (p-0.00) (Table 5).

DISCUSSION

In our study, misoprostol a prostaglandin E1 analogue used as one of the uterotonic agent in the management of third stage of labor is found to be as efficacious and safe drug as other uterotonic agents like syntocinon and syntometrine. The results of a study conducted by Zachariah E[10] are in accordance with our study as far as the blood loss, drop in hematocrit and adverse effects are concerned.

A randomized controlled trial of misoprostol *vs* oxytocin in the active management of third stage of labor was conducted by Oboro VO.[11] He used 600 mcg of misoprostol orally and compared it with intramuscular oxytocin. The rate of postpartum hemorrhage between misoprostol and oxytocin groups were (1% *vs* 0%, respectively), which is comparable to our study

Table 4: Estimation of blood loss in three study groups

	Misoprostol n(%)	*Oxytocin n(%)*	*Syntometrine n(%)*	*p-value*
Estimated blood loss by pre- and postweighed pads				
< 500 ml	108(33.2)	108(33.2)	102(31.4)	0.83
> 500 ml	2(0.6)	2(0.6)	3(0.9)	
Blood loss measured by drop in Hb				
< 500 ml	105(32.3)	107(32.9)	101(31.1)	0.77
> 500 ml	5(1.5)	3(0.9)	4(1.2)	

Table 5: Adverse effects in three study groups

Adverse effects	*Misoprostol*	*Oxytocin*	*Syntometrine*	*p-value*
Nausea n(%)	12(3.6)	27(8.3)	41(12.6)	0.00
Vomiting n(%)	1(0.3)	6(1.8)	27(8.3)	0.00
Shivering n(%)	26(8)	13(4)	14(4.3)	0.00
Fever n(%)				
– Afebrile	67(20.6)	107(32.9)	99(30.4)	
– <100°F	35(10.7)	3(0.9)	0(0)	0.00
– >100°F	99(30.4)	6(1.8)	0(0)	

results (0.6% *vs* 0.6% respectively). The mean drop in hemoglobin in Oboro study was (0.71 gm/dl *vs* 0.68 gm/dl;p = 0.699 respectively), which are in accordance to our study (0.68 g/dl *vs* 0.65 gm/dl; p = 0.106). Shivering was a pronounced side effect in the misoprostol group of his study which was also observed in our study. So if we compare the dosage of misoprostol in both the study groups, a dose of 400 mcg of misoprostol is as efficacious as 600 mcg of misoprostol with comparable side effects.

Calisken E[12] in his study compared 600 mcg misoprostol intrarectally with conventional oxytocics in the treatment of third stage of labor and found out that postpartum hemorrhage was significantly higher (9.8%) in the group that received rectal misoprostol therapy as compared with (3.5%) that received conventional oxytocics which is statistically significant. The high incidence of postpartum hemorrhage in Calisken study might be due to different the route of administration and drug pharmacokinetics. Hence, for the prevention of postpartum hemorrhage oral misoprostol use is preferable than rectal use. Sublingual misoprostol has also been used in the prevention of postpartum hemorrhage by Vimala N[13] after cesarean delivery. In his study the need for additional oxytocic therapy was 16% in misoprostol group and 18% in oxytocin group (p = 0.673). Whereas in our study fewer number of women needed additional uterotonic agents (misoprostol 1.6% *vs* oxytocin 1.6%;p = 0.954). However, the route of administration of misoprostol for the prevention of postpartum hemorrhage and mode of delivery can be the confounding factors for the interpretation of results. In a study conducted by Chhabra S[14] in which he compared 100 mcg, 200 mcg of sublingual misoprostol with methylergometrine for the active management of labor shows insignificant need for administration of additional oxytocics (p = > 0.05). Hence we determine that misoprostol even in a low dose given orally or sublingually, remains a better choice for the prevention of postpartum hemorrhage than other routes of administration.

In our study misoprostol was found to be as effective as oxytocin and syntometrine in the prevention of postpartum hemorrhage. In contrary to that Caliskan E et al[15] found that oral misoprostol alone is as effective as oxytocin alone for the prevention of postpartum hemorrhage but less effective than oxytocin plus methylergonovine maleate and oral misoprostol plus oxytocin. The incidence of postpartum hemorrhage is high in his study with misoprostol alone group when compared to syntometrine (9% *vs* 3.5%; p = 0.01).

Our study shows that the amount of blood loss >500 ml in misoprostol group was (0.6%) for misoprostol and (0.9%) for syntometrine group which are comparable. Similar study was carried out by Enakpene CA et al[16] shows that misoprostol is superior to methylergometrine when compared in regards to mean blood loss as well as blood loss >500 ml which is contrary to the results of our study. The most likely reason for this is that more women in Enakpene study underwent manual removal of placenta in the methylergometrine group when compared to misoprostol group whereas in our study no woman had to undergo manual removal of placenta. This may also be the cause for need of additional oxytocics in his study.

In our study, shivering and fever were the two pronounced side effects associated with misoprostol group when compared to syntocinon alone or syntometrine. The number of women who experienced pyrexia, shivering and metallic taste was significantly higher in misoprostol group in his study which is in accordance to our study. Similar findings have been reported by Oboro VO[11] and Vimala N.[13]

In Pakistan, 80% of women deliver at home with most of the time a having single birth attendant facilitating the delivery. There is a need for safe oral medication which does not need maintenance of cold chain and can be used safely by community midwives in deliveries conducted at home. Misoprostol can replace oxytocin in reducing postpartum hemorrhage in low-risk women, in rural areas with home deliveries, especially as it is thermostable in tropical conditions. So given the advantages of misoprostol stability at room temperature, low cost and easy route of administration it appears to be a better choice for the prevention of postpartum hemorrhage especially at primary level. It is one of the best preventive measures of postpartum hemor-

rhage in conditions where single birth attendant is carrying out the delivery with no facilities for refrigeration. In developing countries like Pakistan, oral misoprostol is a potentially simple, cost effective, safe and effective choice of treatment among the females belonging to every subset of the community.

CONCLUSION

Misoprostol is an efficacious and safe alternative to conventional uterotonic agents in the active management of third stage of labor especially in developing countries both at tertiary and community level.

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