Is Rectally or Orally Administered Misoprostol and Oxytocin Combination More Effective in Prevention of Postpartum Hemorrhage When Compared With Oxytocin Alone?

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Abstract

Objective: To investigate whether the addition of rectally or orally administered misoprostol to the standart oxytocin regimen is more effective or not when compared with the standart oxytocin regimen alone in preventing postpartum hemorrhage.

Methods: In a controlled trial, 1212 women were randomized to receive; 1-) intravenous infusion of oxytocin 10 IU plus 600 μg misoprostol administered via the rectal route, 2-) intravenous infusion of oxytocin 10 IU, and 3-) intravenous infusion of oxytocin 10 IU plus 600 μg misoprostol administered via the oral route. The third stage was managed actively by early cord clamping and controlled cord traction. The main outcome measures were incidence of postpartum hemorrhage (blood loss ≥500 mL) and change in hemoglobin concentration before delivery and 24 hours postpartum.

Results: The incidence of postpartum hemorrhage was 3.2% in Group 3, compared with 8.1% in Group 2 and 6.6% in Group 1 (p=0.002 and p=0.02 respectively). The number of women with postpartum hemorrhage was similar in Group 1 and Group 2. There were no significant differences between the three groups with regard to drop in hemoglobin concentrations. Significantly less women needed additional oxytocin in Group 3 when compared with Group 2 (6.7% vs 2.4%; p= 0.003). The proportion of women requiring additional methylergometrine was significantly reduced in Group 3 when compared with Group 2 and Group 1 (0.7% vs. 3.6%; p=0.004 and 0.7% vs. 2.9%; p=0.01 respectively.

The incidence of blood transfusions in the postpartum period was significantly higher in Group 2 when compared with Group 1 and Group 3 (3.3% vs. 1.0%; p=0.02 and 3.3% vs. 1.2%; p=0.04 respectively).

Conclusion: Concomitant administration of oral misoprostol and oxytocin infusion is superior to oxytocin alone or oxytocin plus rectal misoprostol in controlling postpartum hemorrhage.

Keywords: postpartum hemorhage, oxytocin, misoprostol, oral, rectal

Özet

Oral ya da Rektal Uygulanan Misoprostol ve Oksitosin Kombinasyonu Postpartum Hemorajiyi Önlemede Tek Başına Oksitosinden Gerçekten Daha Etkili midir?

Amaç: Standart oksitosin rejimine oral ya da rektal uygulanan misoprostolün eklenmesinin, postpartum hemorajiyi önlemede tek başına standart oksitosin rejimine göre daha etkili olup olmadığını araştırmak.

Metot: Bu kontrollü çalışmada, 1212 kadın 1-) 10 IU intravenöz oksitosin infüzyonuna ek olarak 600 μg rektal misoprostol, 2-) 10 IU intravenöz oksitosin infüzyonu ve 3-) 10 IU intravenöz oksitosin infüzyonuna ek olarak 600 μg oral misoprostol almak üzere randomize edildi. Doğumun üçüncü evresi erken kord klemplenmesi ve kontrollü traksiyonu yapılarak aktif olarak yönetildi. Ana sonuç parametrelerimiz postpartum hemoraji (kan kaybı ≥500 mL) insidansı ve doğum öncesi ve postpartum 24. saatteki hemoglobin konsantrasyonları arasındaki farktı.

Sonuçlar: Postpartum hemoraji insidansı Grup 3'e göre karşılaştırıldığında (%3.2), Grup 2'de %8.1 ve Grup 1'de %6.6 (sırasıyla p=0.002 ve p=0.02) idi. Grup 1 ve Grup 2'de postpartum hemorajisi olan kadın sayısı benzerdi. Üç grup arasında hemoglobin konsantrasyonundaki düşüş açısından anlamlı farklılık saptanmadı. Grup 2 ile karşılaştırıldığında Grup 3'te ek oksitosin gereksinimi anlamlı olarak düşüktü (%6.7'ye karşılık %2.4; p= 0.003). Grup 2 ve Grup 1 ile karşılaştırıldığında Grup 3'te ek metilergometrin ihtiyacı gösteren kadınların oranı anlamlı olarak azalmıştı (sırasıyla, %0.7'ye karşılık %3.6; p=0.004 ve %0.7'ye karşılık %2.9; p=0.01). Postpartum dönemde yapılan kan transfüzyonu insidansı Grup 2'de Grup 1 ve Grup 3 ile karşılaştırıldığında anlamlı olarak yüksek saptandı (sırasıyla %3.3'e karşılık %1.0; p=0.02 ve %3.3'e karşılık %1.2; p=0.04).

Tartışma: Eşzamanlı oral misoprostol ve oksitosin infüzyonu postpartum hemorajiyi önlemede tek başına oksitosin ya da oksitosin ile birlikte rektal misoprostol uygulanmasına göre daha üstündür.

Anahtar sözcükler: postpartum hemoraji, oksitosin, misoprostol, oral, rektal

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Introduction

Although the incidence of hemorrhage-related maternal deaths has dramatically declined in industrialized countries during the twentieth century (1), postpartum hemorrhage still remains as the leading cause of maternal deaths in the developing world (2). Death due to postpartum hemorrhage accounts for 17% to 40% of the maternal mortality in some parts of the world (2,3). The incidence of death due to postpartum hemorrhage is at least 100 times higher in developing countries than in developed countries (1,4). In Turkey, postpartum hemorrhage accounts for 12.3% of maternal deaths (5).

As postpartum hemorrhage is a major cause of maternal mortality in developing countries, it is important to consider any intervention that may minimize this complication (6). In rural communities, the lack of access to skilled birth attendants who are able to administer parenteral oxytocic agents, the high incidence of anemia in pregnancy, the lack of availability of safe blood transfusion services and the lack of refrigeration to store oxytocic agents worsens the outcome of postpartum hemorrhage (7). The availability of an easily administered, affordable and thermostable preparation for routine management of the third stage of labor may have considerable benefits in preventing postpartum hemorrhage and perhaps reduce maternal morbidity and mortality in the third world, where atonic postpartum hemorrhage is common due to high multiparity and prolonged labor (8).

Current oxytocic drugs are far from ideal, particularly for routine use in developing countries, where simple routes of administration and stable, inexpensive drugs are needed (9). The lack of an easily administered and thermostable uterotonic agent is a major impediment for the prevention of life-threatening postpartum hemorrhage in the developing world (10).

Although the prophylactic use of uterotonics in the third stage has become routine, the preparations used vary from center to center; oxytocin, ergometrine or a mixture of oxytocin and ergometrine are used. In Turkey, active management of the third stage of labor and routine use of oxytocics are not standard practice, especially among midwives, who attend most low risk pregnancies.

Based on their clinical observations, El Refaey et al. (11) have been the first to suggest oral misoprostol as an alternative to conventional standard oxytocic drugs for the prevention of atonic postpartum hemorrhage in low risk women. This was followed by a prospective uncontrolled study by the same group (12). O'Brien et al. (13) have suggested rectally administered misoprostol as a potent uterotonic agent in the management of intractable postpartum hemorrhage unresponsive to oxytocin and ergometrine. Since then, several studies have examined the use of oral and rectal misoprostol in the third stage of labor (6,9,14,15,16).

Although extensive data are available regarding the absorption and pharmacokinetic properties of orally and vaginally administered misoprostol (17), no data is available to date adressing the absorption and pharmacokinetic properties of rectally administered misoprostol. For this reason, the effectiveness of rectal misoprostol for prevention of postpartum hemorrhage still remains as a subject of controversy.

The purpose of this study is to investigate whether the addition of rectally or orally administered misoprostol, given in a total dose of 600 µg, to the standart oxytocin regimen is more effective or not when compared with the standart oxytocin regimen alone in preventing postpartum hemorrhage.

Materials and Methods

The trial was conducted between January 1, 2000 and October 1, 2000, at SSK Maternity and Women's Health Training Hospital, Ankara, Turkey; which is one of the main referral hospitals for metropolitan Ankara, serving an almost entirely population of low socioeconomic status and is the site of more than 20 000 births a year. The maternal mortality rate of this institution was 38 per 100 000 births for 1996-2000. The research protocol was approved by the local research ethics committee. The standard policy to prevent postpartum hemorrhage is intravenous infusion of oxytocin10 IU (Synpitan forte ® Deva Co., Turkey) in 500 cc saline over 30 minutes.

Women in labor were asked to participate in the study and written informed consent was obtained on admission to the labor ward. Exclusion criteria were stated as gestational age <32 weeks, cesarean section and known hypersensitivity to prostaglandins.

Just after consenting, women were allocated by means of sealed opaque envelopes, in computer-generated random sequence. Randomization before entering the labor ward was performed in order to prevent the effect of the variables of the second stage of labor on the decision of the management of third stage. In the third stage of labor, immediately after cord clamping, the women received: **1**- intramuscular administration of 1 ml saline (placebo), intravenous infusion of oxytocin 10 IU in 500 ml saline over 30 minutes, two tablets of misoprostol (400 µg) (Cytotec ® Ali Raif Co., Turkey) administered rectally, followed by two doses of misoprostol 100 µg (µ tablets) administered intrarectally four hours apart, **2**- intramuscular administration of 1 mL saline (placebo), intravenous infusion of oxytocin 10 IU in 500 mL saline over 30 minutes, two tablets of rectally administered placebo (similar in size and color but not the shape), (Placebo, Plantafarma Co., Turkey) followed by µ tablets of placebo administered rectally, **3**- intravenous infusion of oxytocin 10 IU in 500 ml saline over 30 minutes two tablets of misoprostol (400 µg) (Cytotec® Ali Raif Co., Turkey) administered orally, followed by two doses of misoprostol 100 µg (µ tablets) administered orally four hours apart. In

order to overcome the limitation of the shape of the placebo, all medications were applied by midwives but residents who manage the birth and the third stage of labor were blinded to the identity of medication. Only the midwife applying the medication opened the envelope once to read the code and than transferred the randomization code into another identical envelope. The identity of the placebo and active medication were also concealed from caregivers and residents who followed up the patient for the next 24 hours. The randomization code was not broken until the study completion.

The third stage of labor was managed actively by means of early cord clamping and controlled cord traction while gentle uterine massage was performed by the resident. No additional oxytocic drugs except the study medication were administered routinely. If the placenta could not be delivered after 30 minutes, manual removal was performed. The women were carefully observed for features of excessive blood loss; if signs were present, active intervention commenced with intravenous infusion of 20 IU oxytocin in 1000 mL saline over one hour. Intramuscular administration of methylergometrine 0.2 mg was performed whenever an atonic uterus was palpated or bleeding continued despite oxytocin infusion. Blood transfusion was performed to women with postpartum hemorrhage whenever the hemoglobin concentrations were found to be <7.5 g/dL.

The resident physician in charge of labor completed the data collection form. Information on maternal characteristics such as age, parity, body mass index (BMI), gestational age at delivery and reproductive history were included in this form. Variables of labor included induction and augmentation. No epidural analgesia was performed throughout the study period. Variables concerning the delivery included the mode of delivery, the use of an episiotomy, the presence of a perineal tear and birth weight. Patients were evaluated by a resident physician and side effects such as nausea, vomiting, diarrhea, hot flushes, headache, tiredness, dizziness, shivering and hyperthermia (temperature >38°C within 12 hours of delivery) assessed until 24 hours after delivery.

A blood sample for determination of hemoglobin concentration was obtained from consenting women before delivery. A second blood sample for hemoglobin concentration was obtained 24 hours postpartum. Blood loss was estimated by the physician in charge of labor. The blood was collected into a sterile steel bedpan after birth by the help of a plastic bed linen. All gauzes and pads were collected until one hour after the delivery of the placenta and weighed at the end. The difference in grams was considered to be equivalent to the blood loss in milliliters. Postpartum hemorrhage was defined as measured blood loss of ≥500 mL and severe postpartum hemorrhage as blood loss ≥1000 mL. Frequency of blood transfusion, need for additional oxytocic drugs, length of the third stage of labor, subsequent evacuation of uterus, frequency of delayed hemorrhage and incidences of side effects were also recorded.

The main outcomes of the trial were the incidence of postpartum hemorrhage (defined as blood loss ≥ 500 cc) and the drop in hemoglobin concentrations. The secondary outcomes were the incidence of severe postpartum hemorrhage (blood loss ≥1000 mL), need for additional oxytocic drugs, length of the third stage of labor, incidence of delayed hemorrhage, subsequent evacuation of uterus, need for postpartum blood transfusion as well as the incidence of side effects.

Statistical Analysis

The statistical analysis of the data was performed using the Statistical Package for Social Sciences for Windows (SPSS, Chicago, IL, USA). Results were reported as mean ± standard deviation and percentages. Differences between the groups were assessed using chi-square test or Fisher's exact test for categorical data whenever appropriate. In order to detect the differences of continuous variables between the groups, analysis of variance and Tukey tests were used. For all comparisons $p<0.05$ was considered statistically significant.

Results

1212 women completed the study (Group 1, n=401; Group 2, n=407; Group 3, n=404). There were no significant differences between the three groups with regard to maternal demographics (Table 1). The randomization process was successful in producing well-matched groups.

No statistically significant difference was found out when three groups were compared with regard to intrapartum data (Table 2).

The effect of the trial treatments in the third stage of labor is described in Table 3. The incidence of postpartum hemorrhage (blood loss ≥500 cc) was 3.2% (13/404) in Group 3, compared with 8.1% (33/407) in Group 2 (p=0.002) and 6.6% (28/401) in Group 1 (p=0.02). The number of women with postpartum hemorrhage was similar in Group 1 and Group 2. The incidence of severe postpartum hemorrhage (blood loss ≥1000 cc) was higher in Group 2 compared with Group 1 and Group 3 but the difference was statistically significant between Group 2 (14/407, 3.4%) and Group 3 (5/404, 1.2%), (p=0.03).

Less women needed additional oxytocin in Group 3, when compared with Group 1 and Group 2 but the difference was statistically significant only between Group 2 and Group 3 (26/407, 6.7% vs. 10/404, 2.4%; p=0.003, respectively). Significantly less women needed additional methylergometrine in Group 3 when compared with group 2 and Group 1 (3/404, 0.7% vs.14/407, 3.6%; p=0.004, and 3/404, 0.7% vs.12/401, 2.9%; p=0.01, respectively).

The proportion of women requiring blood transfusion in the postpartum period was significantly higher in Group 2 when compared with Group 1 and Group 3 (13/407, 3.3% vs. 4/401, 1%; p=0.02, and 13/407, 3.3% vs. 5/404, 1.2%; p=0.04, respectively).

Table 1. Demographic characteristics of the groups. [Data are presented as mean±standard deviation of the mean or n (%)]

Characteristic	Rectal + oxytocin (n=401)	oxytocin (n=407)	Oral + oxytocin (n=404)
Maternal age (years)*	25.5±5.3	25±5.1	25.6±5
Body mass index*	28.2±3.4	27.9±4.5	28.2±4.6
Parity*	0.8±1	0.7±1	0.8±0.9
Primiparas†	205 (51.1)	194 (47.6)	183 (45.2)
Multiparas†	191 (47.6)	196 (48.1)	217 (53.7)
Grandmultiparas‡	5 (1.2)	7 (1.7)	3 (0.7)
Gestational age (days)*	275±11	275±11.1	276±11.2
Predelivery hemoglobin(g/dL)*	11.3±1.3	11.4±1.3	11.4±1.4
Predelivery hematocrit (%)*	35.2±3.4	35.3±3.4	35.2±3.6
Maternal anemia (Hemoglobin<10 g/dL) †	42 (10.6)	39 (9.5)	46 (11.3)
Antepartum blood transfusion‡	2 (0.5)	5 (1.2)	5 (1.2)

* No statistically significant difference between groups (p>0.05), ANOVA, Tukey's test.
† No statistically significant difference between groups (p>0.05), chi-square test.
‡ No statistically significant difference between groups (p>0.05), Fisher's exact test.

Table 2. Intrapartum data of women receiving rectal misoprostol with or without oxytocin compared with those receiving intravenous oxytocin with or without methylergometrine. [Data are presented as mean±standard deviation of the mean or n (%)]

Variable	Rectal + oxytocin (n=401)	oxytocin (n=407)	Oral + oxytocin (n=404)
Multifetal gestation*	2 (0.5)	4 (1)	4 (0.9)
Hydramnios*	2 (0.5)	4 (1)	2 (0.5)
Preeclampsia*	14 (3.4)	9 (2.2)	16 (3.9)
Preterm delivery*	24 (5.9)	22 (5.4)	19 (4.7)
Intrauterine fetal demise*	2 (0.5)	2 (0.5)	2 (0.5)
Birth weight ≥ 4000 g †	26 (6.4)	24 (5.9)	18 (4.4)
Induction of labor †	48 (11.9)	36 (8.8)	42 (10.3)
Oxytocin augmentation †	263 (65.5)	266 (65.3)	275 (68.1)
Operative deliveries*	13 (3.2)	15 (3.6)	10 (2.4)
Episiotomy †	292 (72.8)	286 (70.2)	304 (75.2)
Perineal tear*	15 (3.7)	11 (2.7)	11 (2.7)

* No statistically significant difference between groups (p>0.05), Fisher's exact test.
† No statistically significant difference between groups (p>0.05), chi-square test.

There were no significant differences between the three groups with regard to drop in hemoglobin concentration and hematocrit; the length of third stage of labor and the incidence of subsequent evacuation of the uterus. The drop in hemoglobin concentration was probably masked by early active intervention in Group 2 with additional oxytocics and blood transfusions.

The incidence of shivering was significantly higher in Group 1 and Group 3 when compared with Group 2 (52/401,12.9% vs. 16/407, 3.9%; p<0.001 and 49/404, 12.1% vs.16/407, 3.9%; p<0.001, respectively). The incidence was similar between Group 1 and Group 3 (p>0.05). Significantly less women experienced hyperthermia (≥38°C) in Group 2, when compared with Group 1 and Group 3 (6/407, 1.4% vs. 19/401, 4.7%; p=0.006 and 6/407, 1.4% vs. 16/404, 3.9%; p=0.02, respectively). There were no significant differences between the three groups with regard to vomiting and diarrhea (Table 4).

Discussion

In countries where many women have severe anemia during pregnancy because of nutritional and enviromental factors, even a relatively small reduction of postpartum blood loss could be clinically relevant (9). The World Health Organization has recommended intramuscular prophylactic administration of oxytocin in the third stage of labor (18).

Table 3. Outcome variables of women receiving rectal misoprostol with or without oxytocin compared with those receiving intravenous oxytocin with or without methylergometrine. [Data are presented as mean±standard deviation of the mean or n (%)]

Variable	Rectal + oxytocin (n=401)	oxytocin (n=407)	Oral + oxytocin (n=404)
Blood loss ≥500 mL[a]	28 (6.6)	33 (8.1)	13 (3.2)
Blood loss ≥1000 mL[b]	11 (2.7)	14 (3.4)	6 (1.4)
Drop in hemoglobin (g/dL)[c]	1.5 ± 1.3	1.4±1.4	1.4±1.3
Drop in hematocrit (%)[c]	4.4±4.1	4.5±3.7	4.2±4
Length of third stage (min)[c]	8.6±3.3	8.7±1.7	8.8±3.8
Third stage ≥30 min[c]	2 (0.5)	2 (0.5)	3 (0.7)
Additional oxytocin[b]	17 (4.2)	26 (6.7)	10 (2.4)
Additional methylergometrine[a]	12 (2.9)	14 (3.6)	3 (0.7)
Subsequent evacuation of uterus[c]	6 (1.4)	4 (1)	2 (0.5)
Postpartum blood transfusion[d]	4 (1)	13 (3.3)	5 (1.2)

[a]No statistically significant difference between group 1 and 2 ($p>0.05$), group 3 is significantly lower than group 1 and group 2 ($p<0.05$).
[b]Group 2 is significantly higher than group 3 ($p<0.05$), no significant difference between group 1 and 2, group 1 and 3 ($p>0.05$).
[c]No statistically significant difference between groups ($p>0.05$).
[d]No statistically significant difference between group 1 and 3 ($p>0.05$), group 2 is significantly higher than group 1 and group 3 ($p<0.05$).

Table 4. Observed side effects in women receiving rectal misoprostol with or without oxytocin compared with those receiving intravenous oxytocin with or without methylergometrine. [Data are presented as n (%)]

Side effects	Rectal + oxytocin (n=401)	oxytocin (n=407)	Oral + oxytocin (n=404)
Shivering †	52 (12.9)	16 (3.9)	49 (12.1)
Vomiting*	3 (0.7)	2 (0.5)	3 (0.7)
Diarrhea*	9 (2.2)	9 (2.2)	13 (3.2)
Hyperthermia (≥ 38°C)	19 (4.7)	6 (1.4)	16 (3.9)

* No statistically significant difference between groups ($p<0.05$), Fisher's exact test.
† No statistically significant difference between group 1 and 3 ($p>0.05$), group 2 is significantly lower than group 1 and group 3 ($p<0.05$).

Active management of the third stage of labor (19) which includes use of oxytocin therapy (20), early cord clamping and placental delivery by controlled cord traction (21) has been demonstrated to be an effective prophylactic measure against postpartum hemorrhage.

Misoprostol offers several advantages over oxytocin or ergometrine, including a shelf life of several years, stability at high temperatures, oral and rectal administration (i.e. it does not require needle or syringe), minimal side effects such as shivering and hyperthermia and that it can be administered to hypertensive patients (6).

Absorption of misoprostol is extremely rapid, being detected in the circulation within two minutes of its oral ingestion (22). When orally administered, the plasma concentration of misoprostol rises quickly, peaks between 12.5-60 minutes after administration, falls steeply by 120 minutes, and remains low thereafter (17). Since postpartum hemorrhage related to uterine atony typically occurs in the immediate postpartum convalescence, delayed absorption would make misoprostol ineffective for this indication. Although the effect of oral misoprostol on the postpartum uterus has been shown to be rapid (23), oral misoprostol 400 µg was reported to be significantly less effective than the traditional uterotonic agents in a recent study (24); suggesting oral misoprostol not to be considered as a viable option for uterotonic agents currently used in the management of the third stage of labor.

The rectal route for misoprostol use has been considered to have several practical advantages (25,26). Gastrointestinal side effects might be reduced and administration in patients who are vomiting, unable to take orally or under anesthesia would be possible. Since side effects of oral misoprostol are essentially gastrointestinal and dose dependent, the rectal route may be associated with fewer side effects. Although the rate of transmucosal absorption of rectally administered misoprostol has not been determined up to date, studies have shown that rectal misoprostol is useful in the management of the third stage of labor and may be effective in the treatment of postpartum hemorrhage (14,26,27).

Bamigboye et al. (26) studied 491 women who randomly received either 400 µg of misoprostol rectally or 1 ampoule of Syntometrine intramuscularly after delivery. Duration of the third stage of labor, postpartum blood loss and postpartum hemoglobin levels were all similar. Diab et al. (27) compared the effectiveness of rectal misoprostol with combined intramuscular oxytocin and ergometrine in the management of the third stage of labor in 145 women. Misoprostol users had lower third stage estimated blood loss and needed less additional oxytocics compared with the groups receiving oxytocin and ergometrine. Postpartum hemoglobin and hematocrit levels were significantly lower in the oxytocin and ergometrine groups than the misoprostol group. Diab et al. (27) concluded that rectal misoprostol might be used safely in the management of the third stage of labor.

Bugalho et al. (14) compared the effectiveness of misoprostol 400 µg administered as a micro-enema versus oxytocin 10 IU in the management of third stage of labor in 663 women. No significant differences were observed between groups before and 72 hours postpartum in mean hemoglobin and hematocrit, on volume of blood loss and duration of the third stage of labor. Rectal misoprostol was reported to be as effective as oxytocin 10 IU intramuscularly for prevention of postpartum hemorrhage (14).

Amant et al. (28) suggested a combination of rapid onset and slow onset uterotonic drugs to be a new future direction in the prevention of postpartum hemorrhage. In this background, we designated the trial regimen for Group 1 in this study. After rectally administered misoprostol 400 µg and intravenous infusion of oxytocin 10 IU over 30 minutes, misoprostol 100 mg was given intrarectally at the 4^{th} and 8^{th} hours after delivery. The rationale for this regimen was to secure a stable plasma concentration of misoprostol resulting with a sustained contraction of the uterus and subsequent reduction of blood loss in the hours after delivery for preventing delayed hemorrhage. The same purpose was established for women allocated to Group 3, in which orally administered misoprostol 400 µg and intravenous infusion of oxytocin 10 IU over 30 minutes was given followed by misoprostol 100 µg given by the oral route at the 4^{th} and 8^{th} hours after delivery.

The incidence of postpartum hemorrhage was significantly low among women treated with orally administered misoprostol combined with the standart oxytocin regimen with the maintenance misoprostol doses (Group 3), when compared with the identical rectally administered misoprostol group (Group 1) and the oxytocin only group (Group 2). The incidence of severe postpartum hemorrhage was also highest in Group 2 and lowest in Group 3, the difference being statistically significant when compared with each other. The incidences of postpartum hemorrhage and severe postpartum hemorrhage were similar in Groups 1 and 2. Our findings are consistent with the previous reports in terms of incidence of postpartum hemorrhage (14,26).

The clinical threshold for additional parenteral oxytocic management has been considered as a subject of controversy in a previous report (26). The oxytocin only group (Group 2) in our study had the highest additional oxytocin requirement rate, compared with other groups where misoprostol administered by the oral or the rectal route was combined with the standart oxytocin regimen. The relatively late onset of action of misoprostol may be argued against its use in the management of the third stage of labor but especially orally administered misoprostol seems to be advantageous in preventing additional oxytocin use resulting from blood loss greater than 500 ml. Similarly misoprostol administered in either route is effective in reducing the need for additional methylergometrine over that observed with oxytocin administered alone. However it should be emphasized that misoprostol administered orally more effectively reduces the need for additional methylergometrine than does misoprostol administered rectally.

However, no differences were found between three groups in terms of drop in hemoglobin and hematocrit concentrations at the 24^{th} hour after delivery. The early active management of excessive bleeding with conventional oxytocics and blood transfusions in Group 2 may have reduced the potential of the study to detect differences between groups with regard to drop in hemoglobin concentrations.

Previous studies reported that the length of the third stage in rectally administered misoprostol groups are similar to conventional oxytocics (14,26). In our study, addition of misoprostol to oxytocin did not cause any difference in the length of the third stage.

Incidence of postpartum blood transfusion was highest in Group 2, the incidence resulting from the high rate of postpartum hemorrhage in the same group.

Side effects associated with orally administered misoprostol in the third stage of labor are well established (6,9,15,28). The side effects associated with orally administered misoprostol were reported to potentially limit the clinical usefulness of the drug particularly when large doses are needed (25). Bugalho et al. (14), reported the incidences of shivering and hyperthermia to be significantly greater among women receiving rectal misoprostol than oxytocin. In the present study, we have found out hyperthermia and shivering to occur significantly more frequently in women treated with misoprostol administered by either route (Group 1 and Group 3), compared with women treated with oxytocin alone (Group 1). The route of administration did not differ significantly in terms of having an effect on the incidence of shivering and hyperthermia. Shivering and hyperthermia were observed to be well-tolerated side effects in the current study and seemed to be dose-related; consistent with the original findings of El-Refaey et al. (12).

There are two major limitations associated with the current study. First, the trial is not double blinded because of the

unability to get identical placebo tablets. However, this was minimized by having an independent nursing staff in the preperation and administration of the medications. The second is the unability to eliminate the use of additional oxytocics and blood transfusions resulting with a probability of masking the drop in hemoglobin concentrations between the groups.

Our study showed that 600 µg misoprostol administered by the oral or rectal route in addition to the standart 10 IU oxytocin regimen is more effective in prevention of postpartum hemorrhage, than the standart 10 IU oxytocin regimen alone; pointing out that concomitant administration of oral misoprostol and oxytocin infusion is superior to oxytocin alone or oytocin plus rectal misoprostol in controlling postpartum hemorrhage.

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