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Prophylactic misoprostol for the prevention of postpartum hemorrhage: a randomized controlled trial

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Abstract. – OBJECTIVE: Postpartum hemorrhage (PPH) is one of the major preventable causes of maternal death in developing countries. Although the non-parenteral use of misoprostol is a big advantage especially in home births, its benefits in prevention of PPH is still debating. We aimed to assess the effect and side-effects of prophylactic oral, rectal or vaginal misoprostol on preventing postpartum hemorrhage comparing with no-treatment option.

PATIENTS AND METHODS: In a randomized clinical trial, during uncomplicated vaginal delivery, 248 women were assigned to receive one of the five treatment protocols in the third stage of labor which was managed routinely by early cord clamping and controlled cord traction. Maternal hemoglobin and hematocrit values, the duration of the third stage, and the incidence of blood transfusion was recorded.

RESULTS: There was no statistically significant differences between the antepartum and postpartum values of hemoglobin or hematocrit between the groups. The mean duration (11.8±4.5 min) of the third stage of labor in oral+vaginal group was significantly shorter. Shivering was observed totally in 11 women and the differences were not significant between groups.

CONCLUSIONS: Despite misoprostol has benefit in treatment of postpartum hemorrhage, it has no remarkable effect in prophylaxis of atony-induced postpartum hemorrhage.

Key Words:
Prophylactic, Misoprostol, Postpartum hemorrhage, Vaginal, Rectal, Oral.

Introduction

The leading causes of pregnancy-related deaths are hemorrhage, embolism and hypertensive disorders of pregnancy. Postpartum hemorrhage is a major preventable cause of maternal morbidity and mortality in developing countries[1]. Although the hemorrhage-related mortality ratios have decreased over the past 20 years, postpartum hemorrhage accounts for more than one-quarter of maternal deaths[2]. The decrease in antenatal deaths is related to several strategies that comprise "active management of the third stage of labor", which includes early cord clamping and controlled cord traction and administration of oxytocin with or without ergometrine[3-5]. Use of oxytocin alone or in combination with ergometrine increases the risk of unpleasant and occasionally dangerous side effects such as nausea, vomiting, hypertension, intra-cerebral hemorrhage, myocardial infarction, cardiac arrest, pulmonary edema and neonatal convulsions[6,7]. Misoprostol is an orally administered synthetic prostaglandin E_1 analogue that was originally developed for the prophylaxis or treatment of peptic ulcer disease. The usage of misoprostol in Active Management of the Third Stage of Labor (AMTSL) in developing countries was first reported in 1996 by El-Refaey et al[8]. Since then, many researchers have investigated the efficiency, routes of administration, side effects and usage in prevention or treatment of obstetric hemorrhage. Misoprostol is generally well tolerated and has no major side effects. The most commonly reported side effects are shivering, nausea, vomiting and pruritus. Misoprostol is absorbed quickly when administered orally, sublingually, vaginally or rectally[9,10]. Vaginal or rectal application was found to be superior in some trials and is believed to lessen gastrointestinal side effects[11,12]. In cases where general anesthesia and vaginal bleeding make oral and vaginal administration impossible, rectal administration is appropriate. Many studies have suggested that misoprostol is effective in the prevention of postpartum hemorrhage[13-16], though some placebo-controlled trials have reported opposite results[17].

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Given these discrepancies, the aim of this study was to investigate the effects and side effects of oral, vaginal and rectal misoprostol compared with no treatment in preventing postpartum hemorrhage in the third stage of labor.

Patients and Methods

A total of 248 women were recruited for the study. All women who were admitted for delivery at the Uludag University Teaching Hospital in Bursa, Turkey were evaluated for eligibility, and patients provided written informed consent. The criteria for exclusion were refusal to participate, placenta previa, previous PPH (postpartum hemorrhage), antepartum hemorrhage after 20 weeks of gestation, non-cephalic presentation, multiple pregnancy, intrauterine death, parity greater than five, uterine fibroid, anticoagulation therapy, preeclampsia and women undergoing cesarean delivery.

During labor, subjects were randomly assigned using random number-generated tables to one of the following five groups for the management of the third stage of labor: the control group received no treatment (n=49); group 1 received a single oral dose of 400 mg of misoprostol (n=50); group 2 received an oral dose of 400 mg of misoprostol plus a vaginal dose of 400 mg of misoprostol (n=48); group 3 received a single rectal dose of 400 mg of misoprostol (n=50); and group 4 received a vaginal dose of 400 mg of misoprostol (n=51)]. Any uterotonic drugs could be administered in the control group. The third stage of labor in all groups was managed routinely by early cord clamping and controlled cord traction. The misoprostol tablets were assigned randomly within 1 minute of the baby's birth, immediately after cord clamping. For vaginal application, the tablet was placed in the posterior fornix of the vagina. No additional oxytocic drugs were administered routinely. The women were carefully observed for features of excessive blood loss. Ergometrine and oxytocin were administered only if the blood loss observed appeared to be greater than usual. Maternal hemoglobin and hematocrit values were measured prenatally and at 24 hours postpartum. Perineal trauma (episiotomy, first or second degree tear) and the duration of the third stage of labor were recorded. Side effects, including nausea and vomiting, shivering, diarrhea, and abdominal pain, were noted. The primary outcome was postpartum blood loss as estimated by antepartum and postpartum hemoglobin and hematocrit values. Secondary outcomes included the duration of third stage of labor, the need for blood transfusion and the need for uterotonic agents to control postpartum hemorrhage.

Statistical Analysis

SPSS 10.0 for Windows (Statistical Package for the Social Sciences; SPSS Inc., Chicago, IL, USA) was used for all statistical analysis. Entry characteristics (non-parametric values) were compared using the Kruskal-Wallis test, and gestational age and other measurements (parametric values) were analyzed with ANOVA. An LSD test was used for many-sided comparison. A two-sided p value < 0.05 was considered to be statistically significant.

Results

Among the 248 women, none withdrew from the study after randomization. Table I shows that the baseline and labor variables were similar in all groups. The primary outcomes are shown in Table II. There were no statistically significant differences in the antepartum and postpartum values of hemoglobin and hematocrit between the groups when compared with the control group.

The mean duration (11.8±4.5 min) of the third stage of labor in group 2 was significantly shorter than that in the control group (14.8±5.0 min; p=0.001), group 3 (14.8±5.0 min; p=0.001) and group 4 (13.6±5.0 min; p=0.04).

The mean changes in antepartum compared to postpartum hematocrit and hemoglobin values did not differ between the groups. Oxytocin was required by one woman in each of groups 1, 2, and 3 and by three women in group 4. Blood transfusion was performed for one woman in each of groups 1, 2 and 3, and the incidences among the groups did not differ significantly.

There were no episodes of diarrhea or abdominal pain among the women. Shivering was observed in one woman in the control group, three women in groups 1 and 4 and two women in groups 2 and 3. These differences were not significant (Table III).

Discussion

Postpartum hemorrhage remains the most common cause of maternal mortality world-

Table I. Baseline and labor variables.

	Control group No treatment (n = 49)	Group-1 Oral 400 μg (n = 50)	Group-2 Oral 400 μg + Vaginal 400 μg (n = 48)	Group-3 Rectal 400 μg (n = 50)	Group-4 Vaginal 400 μg (n=51)	$p < 0.05$
Gravidity	2.2 ± 1.1	2.0 ± 1.5	2.2 ± 1.4	2.2 ± 1.4	1.9 ± 1.0	NS
Parity	0.8 ± 0.7	0.6 ± 0.9	0.8 ± 1.0	0.8 ± 1.1	0.5 ± 0.6	NS
1st- stage labor duration (hour)	7.4 ± 3.3	7.7 ± 3.3	7.0 ± 2.9	7.0 ± 3.0	7.1 ± 2.8	NS
2nd- stage labor duration (hour)	1.1 ± 1.3	0.9 ± 0.9	0.7 ± 0.5	0.8 ± 0.7	0.8 ± 0.5	NS
Gestational age (week)	37.8 ± 3.5	37.1 ± 4.4	38.6 ± 9.9	36.6 ± 4.7	37.4 ± 4.2	NS
Hemoglobin (g/dL)	11.9 ± 1.2	11.9 ± 1.5	11.7 ± 1.5	11.7 ± 1.4	11.8 ± 1.8	NS
Hematocrit (%)	36.1 ± 4.1	35.5 ± 4.2	35.3 ± 4.5	34.7 ± 3.9	35.6 ± 4.7	NS
Perineal trauma*§	48/49	(97.9)	49/50	(98.0)	47/48	NS
n (%)	(97.9)	48/50	(96.0)	49/51	(96.0)	NS

*Value expressed as the mean value ± SD or numbers with percentage in parentheses. §Episiotomy and 1st or 2nd degree tear

wide[1,2,18]. A large multi-country survey conducted by the WHO showed that among 275 000 births, 1.2% of women experienced PPH, yielding an overall PPH death rate of 38 per 100 000 births. Of women with PPH, 18% had a severe maternal outcome, and 3% died[19]. The outcomes from PPH may be improved with prevention and treatment. The most important point of prevention is to manage the third stage of labor, and uterotonics can play a major role in this period. Oxytocin and ergometrine are being used widely, and misoprostol remains under investigation for the prevention of PPH. Although the ability to administer misoprostol orally, sublingually, vaginally and rectally makes it attractive for use, many questions remain to be answered. We attempted to answer the following questions:

1. Does misoprostol as a prophylactic agent to prevent atony have an advantage over no treatment?
2. Which route and dosage is the most effective and has the fewest side effects?

Does Misoprostol as a Prophylactic Agent to Prevent Atony have an Advantage Over no Treatment?

There is no consistent answer to this question in the literature. Some research shows that it reduces postpartum blood loss[8,14,15,17,20], but other research suggests that it is not as effective as oxytocin[21,22]. The trials assessing the effect of misoprostol on the prevention of postpartum hemorrhage in situations where oxytocin is not available show variable results and variable effects on PPH rates[23]. Three trials used 600 μg of misoprostol administered orally or sublingually in community or primary healthcare settings without access to conventional injectable uterotonics. The first was a randomized trial of 661 women attended by midwives in a primary health center in Guinea-Bissau[24]. Findings indicated that 600 μg of sublingual misoprostol was significantly better than placebo at reducing severe PPH (blood loss ≥1000 mL). The second, involving 1 620 home births attended by auxiliary

Table II. Primary outcomes.

	Control group No treatment (n = 49)	Group-1 Oral 400 μg (n = 50)	Group-2 Oral 400 μg + Vaginal 400 μg (n = 48)	Group-3 Rectal 400 μg (n = 50)	Group-4 Vaginal 400 μg (n=51)	$p < 0.05$
Hemoglobin difference* (g %)	-8.8 ± 1.7	-10.4 ± 1.4	-10.4 ± 2.7	-7.2 ± 1.7	-8.0±1.4	NS
Hematocrit difference* (%)	-10.3 ± 1.8	-9.7 ± 1.4	-7.1 ± 1.6	-6.9 ± 2.0	-6.8±1.3	NS

Data are presented as the mean ± standard error of the mean (%). *Difference between values measured before and 24 hours after delivery.

Table III. Primary outcomes.

	Control group No treatment (n = 49)	Group-1 Oral 400 μg (n = 50)	Group-2 Oral 400 μg + Vaginal 400 μg (n = 48)	Group-3 Rectal 400 μg (n = 50)	Group-4 Vaginal 400 μg (n=51)	$p < 0.05$
3rd- stage labor duration (min)	14.1 ± 4.0[a]	12.4 ± 4.0[b]	11.8 ± 4.5[a, c, d]	14.8 ± 5.0 [b,c]	13.6 ± 5.0[d]	$p < 0.05$
Need for uterotonic	0/49	1/50	1/48	1/50	2/51	NS
Blood transfusion	0/49	0/50	1/48	1/50	1/51	NS
Shivering	1/49	3/50	2/48	2/48	3/51	NS

Value expressed as the mean ± SD; [a,b]$p = 0.01$; [c]$p = 0.001$; [d]$p = 0.04$

nurse midwives in rural India, showed 600 μg of oral misoprostol to be significantly better than placebo at reducing most indicators of PPH[25]. The third, involving 1119 home births attended by TBAs in Pakistan, showed that compared with placebo, 600 μg of oral misoprostol significantly reduced the rate of PPH (≥500 mL) (16.5% vs. 21.9%; RR 0.76, 95% CI, 0.59-0.97) and the incidence of postpartum declines in hemoglobin greater than 3 g/dL[20].

In a multicenter study by Gulmezoglu et al[21], 9 264 women from nine different countries were assigned misoprostol, and 9 266 were assigned oxytocin. Three hundred sixty-six (4%) women administered misoprostol had a measured blood loss of 1 000 mL or more compared with 263 (3%) women administered oxytocin (RR 1.39 $p<0.0001$). There were 1 398 (15%) women in the misoprostol group and 1 002 (11%) in the oxytocin group who required additional uterotonics (1.40 [1.29-1.51], $p<0.0001$).

A systematic review of 16 randomized controlled trials (RCTs) of misoprostol compared to injectable uterotonics involving a total of 29 042 women[23] has shown that oral misoprostol is less effective than injectable uterotonics in preventing severe PPH (blood loss >1000 mL: 3.3% vs. 2.4%, RR 1.32; 95% CI, 1.16-1.51).

In the Cochrane review published in 2013[26], 78 studies (59 216 women) were included, and 34 studies were excluded. There was no statistically significant difference in maternal mortality for misoprostol compared with the control groups overall (31 studies; 11/19 715 vs. 4/20076 deaths; rRR 2.08; 95% CI, 0.82 to 5.28), for the trials of misoprostol compared to placebo (10 studies; 6/4 626 vs. 1/4 707; RR 2.70; 95% CI, 0.72 to 10.11) or for the trials of misoprostol compared to other uterotonics (21 studies; 5/15 089 vs. 3/15 369 (19/100000); RR 1.54; 95% CI, 0.40 to 5.92). All 11 deaths in the misoprostol arms occurred in studies that used doses of misoprostol ≥ 600 μg.

Oxytocin is, therefore, recommended over misoprostol as a first line drug for PPH prophylaxis[27,28]. However, misoprostol may be of benefit in settings with poor health services where there is limited provision of both refrigerators and skilled birth attendants. In our study, we could not find any differences between the group in terms of percent change in hemoglobin or hematocrit, need for other oxytocic drugs or the incidence of blood transfusions, which means that prophylactic misoprostol is not necessary to prevent atony.

Which Route and Dosage is the Most Effective and has Fewer Side Effects?

The optimal dosage and route of prophylactic misoprostol is not known, but studies have used mainly oral, rectal, vaginal or sublingual doses of 400 μg or 600 μg for prophylaxis[18]. The onset and duration of action is 8 min-2 h orally, 11 min-3 h sublingually, 20 min-4 h vaginally and 100 min-4 h rectally[29]. It is expected that the most effective routes are oral and sublingual because these routes have the shortest onset of action.

Ugwu et al[30] aimed to compare the efficacy of sublingual misoprostol combined with intravenous oxytocin to oxytocin alone in reducing blood loss during and following caesarean section. Intraoperative and postoperative blood loss was significantly lower in Group B (451.3 mL vs. 551.2 mL; 22.7 vs. 42.2 mL, respectively). The need for additional uterotonics was greater in the oxytocin group (66.7% vs. 27.6%). The addition of sublingual misoprostol to intravenous oxytocin reduces postpartum blood loss and the need for additional uterotonics.

A study by Favole et al[31] assessed the effects of 400 μg of sublingual misoprostol plus routine uterotonics on postpartum hemorrhage. In total,

672 women received misoprostol, and 673 received placebo. Misoprostol plus routine uterotonics reduced postpartum blood loss, but the effect was not significant for blood loss of at least 500 mL or blood loss of at least 1000 mL. Misoprostol also reduced the need for non-routine oxytocin, manual removal of the placenta, and hysterectomy, but these differences were not significant.

Hofmeyr et al[32] conducted a study to assess the effectiveness and safety of misoprostol in addition to routine uterotonic therapy as part of the active management of the third stage of labor among 1 103 women at 4 hospitals in South Africa, Uganda, and Nigeria. Participants received a sublingual dose of 400 μg of misoprostol or a placebo in addition to standard active management of the third stage of labor after vaginal birth. The difference in the primary outcome of blood loss of 500 mL or more within 1 hour of randomization was not significant between the 2 groups (misoprostol 22/546 [4.0%] vs. placebo 35/553 [6.3%]).

Chaudhuri et al[33] investigated the effects of mifepristone combined with oxytocin in high-risk patients. In this prospective, randomized, double-blind, placebo-controlled trial, participants were randomly assigned (1:1) to receive 400 μg of sublingual misoprostol or matched placebo following delivery. All participants received 20 IU of oxytocin. Mean intraoperative blood loss was significantly lower in the misoprostol group (505.4 ± 215.5 mL) than in the placebo group. Mean postoperative blood loss was slightly lower in the misoprostol group (96.9 ± 57.3 mL) than in the placebo group. The authors concluded that misoprostol as an adjunct to oxytocin appeared to more effectively reduce blood loss than oxytocin alone.

In another study by Tewatia et al[34], 100 patients with no risk factors for PPH were randomly allocated to receive 600 g of sublingual misoprostol or 10 IU of intravenous oxytocin immediately following delivery. They found that mean blood loss was significantly lower in the oxytocin group.

Bellad et al[35] investigated the effects of sublingual misoprostol compared to standard care using 10 IU of intramuscular (IM) oxytocin. The mean blood loss was 192±124 mL (n=321) among women receiving sublingual misoprostol and 366±136 mL among women receiving oxytocin IM. The incidence of PPH was 3.1% with misoprostol and 9.1% with oxytocin (p=0.002). No woman lost >1000 mL of blood. The investigators observed that 9.7% and 45.6% of women experienced a hemoglobin decline of >10% after receiving misoprostol and oxytocin, respectively.

Mounsuri et al[36] compared rectal to oral misoprostol among 658 patients who were randomly allocated to receive either 600 μg of misoprostol orally or rectally 5 min after cord clamping and cutting. They found that oral administration was associated with significantly more blood loss than rectal administration (p=0.016). They concluded that rectal misoprostol is effective in the management of third stage of labor and has significantly fewer side effects.

Ozkaya et al[37] compared vaginally administered misoprostol to rectally administered misoprostol in a prospective randomized placebo-controlled study. One hundred fifty women with singleton vaginal deliveries were randomized (50 women in each arm) to receive 400 μg misoprostol tablets intravaginally or 400 μg misoprostol tablets rectally. The estimated blood loss, and the drop in hemoglobin and hematocrit values, did not differ between the three groups.

Mirteimouri et al[38] from Iran evaluated the efficacy of rectal misoprostol for the prevention of postpartum hemorrhage. This double-blind randomized clinical trial included full-term pregnant women who were candidates for vaginal delivery. Women were randomly divided into two groups to receive rectal misoprostol or oxytocin. The women in the misoprostol group received 400 μg of rectal misoprostol after delivery, and the women in the oxytocin group received 3 IU of oxytocin in 1 L of ringer serum administered intravenously. The proportion of women who lost > 500 cc of blood was significantly higher in the oxytocin group compared with the misoprostol group (33% vs. 19%) (p=0.005). Additionally, the need for excessive oxytocin for management of postpartum hemorrhage was significantly lower in the misoprostol group than in the oxytocin group (18% vs. 30%) (p=0.003). A decrease in hematocrit was significantly more frequent in the oxytocin group compared with the misoprostol group (mean decrease in hematocrit was 1.3 ± 1.6 in the misoprostol group and 1.6 ± 2.2 in the oxytocin group). The two groups were similar in terms of side effects. They concluded that compared with oxytocin, rectal misoprostol can decrease postpartum hemorrhage and prevent a decrease in hemoglobin.

Elsedeek[39] examined the effects of rectal misoprostol during and after elective cesarean delivery using a study group (n=200) that received 400 μg of misoprostol. The control group (n = 200) re-

ceived a placebo. The mean intra-operative and postpartum blood loss was significantly lower in the study group compared with the control group: 429 ± 234 mL and 185 ± 95 mL vs. 620 ± 375 mL and 324 ± 167 mL, respectively (*P*=0.001 for both comparisons). The difference between the preoperative and postoperative hematocrit values were also significantly lower in the study group than in the control group (4.62 ± 2.45 vs. 8.15 ± 3.84; $p = 0.02$). They concluded that preoperative treatment with 400 μg of rectal misoprostol significantly reduced blood loss related to elective cesarean delivery.

In our study, we did not find any statistically significant differences between the groups that received misoprostol and the control group. The only statistically significant finding was that the duration of the third stage of labor was shorter in group 2, which consisted of both oral and vaginal misoprostol. We could not find any reports in the literature regarding the duration of the third stage of labor among patients receiving misoprostol. This result may be caused by the increased contractions of the myometrium.

The other issue is the dosage of misoprostol. In a meta-analysis by Hofmeyr and Gulmezoglu[40], the direct and adjusted indirect comparisons between 600 and 400 μg of misoprostol showed very similar effectiveness.

There is evidence that lower doses of misoprostol are as effective and have fewer side effects, which have caused calls for the use of reduced dosages[41,42]. In our study, we used dosages of 400 mg in 3 groups and 800 mg (400 mg oral, 400 mg vaginal) in 1 group; we did not find any differences in terms of effects or side effects.

Shivering, chills, and/or fever are reported as common side effects of misoprostol. Shivering is the most common adverse effect and is occasionally accompanied by fever. In the large WHO multicenter study[21] that used 600 μg of oral misoprostol, shivering was experienced by 18% of women, but temperatures of over 38 °C or 40 °C were found in only 6% and 0.1% of women, respectively. Similarly, when Derman et al[25] used 600 μg of misoprostol in rural India, shivering occurred in 52.2% of women, but fever occurred in only 4.2%. Shivering is self-regulating, and even if high temperatures occur, they are transient and resolve with reassurance and symptomatic treatment. Transient diarrhea, nausea, and vomiting may occur following misoprostol administration, but these are rare and occur in less than 1% of women[21].

In the Cochrane analysis[22] published one year ago, pyrexia > 38°C was higher with misoprostol compared with controls (in 56 studies, 2 776/25 647 (10.8%) vs. 614/26 800 (2.3%); average RR 3.97, 95% CI 3.13 to 5.04). The effect was greater for trials using 600 μg of misoprostol or more (27 studies; 2 197/17 864 (12.3%) vs. 422/18 161 (2.3%); average RR 4.64; 95% CI 3.33 to 6.46; than for those using 400 μg of misoprostol or less (31 studies; 525/6 751 (7.8%) vs. 185/7 668 (2.4%); average RR 3.07; 95% CI 2.25 to 4.18.

Conclusions

We found no benefit in terms of prevention of postpartum uterine atony when using misoprostol as a prophylactic agent. There were also no differences between the routes of administration. We could say that misoprostol is not beneficial for the prophylaxis of atony, despite it is beneficial for treating postpartum hemorrhage based on the literature.

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