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ORIGINAL ARTICLE

The effect of prophylactic oral tranexamic acid plus buccal misoprostol on blood loss after vaginal delivery: a randomized controlled trial

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ABSTRACT

Objective: The objective of this study is to evaluate the effect of prophylactic oral tranexamic acid (TA) plus buccal misoprostol on the amount of blood loss after vaginal delivery in women at low risk for post-partum hemorrhage (PPH).

Materials and methods: The study was a randomized open label clinical trial conducted in a tertiary University Hospital between January 2016 and June 2017. We included women who delivered vaginally with a singleton pregnancy. They were randomized into three groups: group I (women received 10 IU oxytocin IV after delivery of the baby), group II (women received 600 μg buccal misoprostol after delivery of the baby), and group III (women received 1000 mg oral TA at the end of the first stage of labor plus 600 μg buccal misoprostol after delivery of the baby). In each group, pre- and post-delivery pulse rate, blood pressure, temperature, and hemoglobin level were evaluated. Additionally, the amount of blood loss, need for blood transfusion, need for additional uterotonics, and side effects of the study medications were recorded.

Results: There was a statistically significant lower hemoglobin level and higher blood loss in the misoprostol group compared with oxytocin group and TA plus misoprostol group ($p = .0001$). There was a statistically significant higher hemoglobin level and lower blood loss in the TA plus misoprostol group compared with the oxytocin group ($p = .004$ and .043, respectively). PPH occurred in 16.7% of women in the misoprostol group compared 1.7% in the oxytocin group and no cases of PPH in the TA plus misoprostol group ($p = .0001$).

Conclusions: In settings like rural area or home delivery in which oxytocin is not available, alternative oral TA plus buccal misoprostol may be considered as an effective line in prevention of PPH.

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Misoprostol; post-partum hemorrhage; tranexamic acid; vaginal delivery

Introduction

Excessive bleeding at or after childbirth accounts for about half of all the post-partum maternal deaths in developing countries, and is the single most important cause of maternal mortality worldwide [1]. Post-partum hemorrhage (PPH) is the major contributor to maternal mortality worldwide representing at least 25% of the maternal deaths annually [2]. Prevention of PPH has become a global aim to reduce maternal mortality. Uterine atony is the main cause of PPH; therefore, active management of the third stage of labor has emerged as a most actual tool in its prevention [3]. Previous study in Egypt recorded that 88% of deaths from PPH occur within 4 h of delivery [4].

Tranexamic acid (TA) is an antifibrinolytic agent that blocks the lysine-binding site of plasminogen to fibrin. Accordingly, clot breaks down, fibrinolysis is inhibited, and excessive bleeding is reduced. In previous studies, its safety has been confirmed for use in non-pregnant women, with no thromboembolic complications [5]. TA is an inexpensive, widely available medicine that has been shown to reduce bleeding in surgery and reduce the risk of death in bleeding trauma patients [6].

TA given at the time of delivery could prevent severe PPH. Plasma t-PA (the main fibrinolytic activator) doubles within an hour of delivery, probably due to the trauma of childbirth [7]. The absolute bioavailability of TA has been reported to be nearly 34%. Following administration of oral TA, peak plasma concentrations are reached within 3 h.

Misoprostol is a prostaglandin E_1 analog that was has proven effects on uterine contractility and cervical ripening; therefore, many trials and systematic reviews have evaluated its use in obstetric and gynecologic procedures [8–10]. Misoprostol is inexpensive, stable at room temperature, and available in more than

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80 countries, making it particularly useful in resource-poor settings [11].

Misoprostol is effective when given orally, buccal, sublingually, vaginally, or rectally, so it might be used by traditional birth attendants, or self-administered, in cases of home-births occurred without attendance of health personnel or where women are at most risk for occurrence of severe PPH [12].

So, the current study aims to evaluate effect of prophylactic oral TA plus buccal misoprostol in the prevention of primary PPH after routine active management of the third stage of labor in women at low risk for uterine atony in comparison with oxytocin and buccal misoprostol alone.

Materials and methods

Study type and settings

This study was a randomized open label clinical trial conducted at a tertiary University Hospital from January 2016 to June 2017. The Institutional Ethical Review Board approved the study, and we obtained a written informed consent from all participants before enrollment.

Study participants

All women admitted to the reception unit for vaginal delivery were invited to participate in the study. We included women aged (20–35 years) with a singleton pregnancy in a cephalic presentation between 38 and 42 weeks gestation.

The participated women were entered the screening phase of the study. This phase included history taking (age, parity, and gestational age) with measurement of weight, temperature, and initial hemoglobin level.

We excluded women with medical disorders such as cardiac, hepatic, renal, neurologic disorders thromboembolic disease, blood disorders, diabetes, gestational hypertension, and pre-eclampsia. Women at risk for PPH as grand multipara (parity >5), multiple pregnancy, polyhydramnios, fetal macrosomia, antepartum hemorrhage, prolonged, and obstructed labor were also excluded. Moreover, we excluded women with scarred uterus or previous instrumental delivery and those suffering from hypersensitivity to TA.

Randomization

A statistician prepared computer-generated randomization tables and placed the allocation data in serially numbered closed opaque envelopes. Each envelope had a card noting the intervention type inside. The envelopes were opened only by the principal investigator administering the study medications according to the order of attendance of women. After acceptance of eligible women to participate in the study, we assigned them randomly in a 1:1:1 ratio to the three arms of the study.

Intervention

The eligible women were allocated to one of the three study groups: group I (oxytocin group) received 10 IU oxytocin IV after delivery of the baby, group II (misoprostol group) received 600 μg buccal misoprostol after delivery of the baby, and group III (TA plus misoprostol group) received 1000 mg oral TA at the end of the first stage of labor plus 600 μg buccal misoprostol after delivery of the baby. A buccal route, in which the tablets are placed in the cheek for 30 min after which any remnants are swallowed.

Follow-up schedule

Immediately after delivery of the baby, and after liquor drainage, the patient was placed over a blood drape of known weight and a graduated container was placed under the delivery bed to collect blood. The amount of blood collected in the blood drape was measured. Then the patient was given preweighed pads, which were weighed 4 h post-partum.

The blood loss was measured by measuring the blood collected in the drape and by weighing the pads before and after delivery. Blood loss from delivery of the baby to 4 h post-partum was calculated. Total blood loss was measured by adding the volume of the contents of the graduated container and the difference in weight (in grams) between pad weight after 4 h and pad weight prior to use (1-g is equivalent to 1 ml).

The patient's pulse rate, blood pressure, and temperature were recorded pre- and post-delivery. Additionally, hemoglobin level was measured in all participants predelivery and 24 h postdelivery and the change in concentration was noted. The need for additional uterotonics, need for blood transfusion, and side effects such as nausea, vomiting, and diarrhea were recorded.

Study outcomes

The primary outcome was the difference in the mean blood loss at 4 h post-partum between the three

groups. The secondary outcomes included the difference in hemoglobin level, the mean difference of pulse and blood pressure measurements, the need for additional uterotonics, need for blood transfusion, and side effects of the study medications.

Sample size

The required sample size was calculated based on previous study assessing the mean blood loss with oral misoprostol. Aziz et al. [13] reported that the mean blood loss with oral misoprostol was 302.8 ± 160.4 ml. We assumed that a 20% decrease in blood loss with an addition of TA will be clinically significant. Using a 90% power with α error of 0.05, a sample size of 120 women was needed in each group (OpenEpi, version 3, open source calculator-SS Mean, SPSS Inc., Chicago, IL).

Statistical analysis

Data were entered and statistically analyzed using the Statistical Package for Social Sciences (SPSS) version 22 (SPSS Inc., Chicago, IL). Qualitative data were described as numbers and percentages. Chi-square test was used for comparison between groups. Quantitative data were described as means (SD) or median (range), as appropriate. One-way ANOVA test was used for comparison between the three groups while Student's *t*-test was used for comparison between each other group. For analysis, $p < .05$ was considered to be significant.

Results

One thousand two hundred women were approached to participate in the study. Eight hundred forty women have been excluded: 805 women were not eligible for inclusion and 35 women declined participation in the study. We randomly assigned the remaining 360 women into the three study groups (Figure 1, the study flowchart).

There were no significant differences between the three groups with regard to their age, parity, weight, gestational age, predelivery temperature, pulse, systolic blood pressure (SBP), diastolic blood pressure (DBP), and initial hemoglobin level (Table 1).

There was a statistically significant increase in the postdelivery pulse rate in the misoprostol group compared with the oxytocin group ($p = .0001$) and TA plus misoprostol group ($p = .0001$). Additionally, there was a significant decrease in the postdelivery pulse rate in the TA plus misoprostol group compared with the oxytocin group ($p = .003$). There were statistically significant decrease in the postdelivery SBP and DBP in the misoprostol group compared with the oxytocin group ($p = .0001$) and the TA plus misoprostol group ($p = .0001$).

There was a significant increase in the postdelivery temperature in the misoprostol group compared with

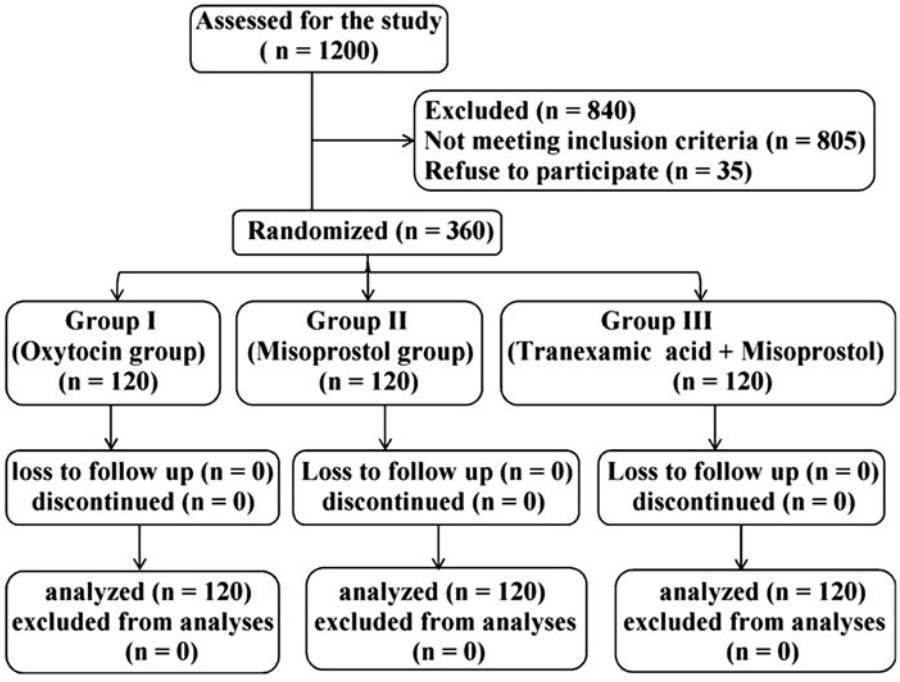

Figure 1. The study flowchart.

Table 1. Characteristics of the study participants.

Characteristics	Oxytocin group ($n = 120$)	Misoprostol group ($n = 120$)	TA plus misoprostol group ($n = 120$)	p Value
Age (years)	28.8 ± 5.12	28.3 ± 4.71	27.8 ± 4.46	.631
Weight (kg)	76.1 ± 9.68	75.5 ± 6.13	75.6 ± 5.18	.805
Parity[a]	2 (0–4)	2 (0–3)	2 (0–3)	.105
Gestational age (weeks)	38.43 ± 5.63	39.58 ± 0.87	39.55 ± 0.85	.215
Pulse	79.54 ± 4.93	79.88 ± 5.12	78.61 ± 5.09	.133
Temperature	36.99 ± 0.14	36.98 ± 0.17	36.98 ± 0.12	.622
SBP	120.3 ± 2.45	119.9 ± 2.49	120.1 ± 2.28	.394
DBP	78.13 ± 2.97	78.19 ± 3.12	78.52 ± 3.08	.569
Initial hemoglobin (%)	10.52 ± 1.06	10.88 ± 0.79	10.61 ± 0.98	.222

TA: tranexamic acid; SBP: systolic blood pressure; DBP: diastolic blood pressure.
All variables are presented as mean and standard deviation.
[a]Data are presented as median (range).

Table 2. The post-partum vital signs, hemoglobin level, and estimated blood loss in the study groups.

Variables	Oxytocin group ($n = 120$)	Misoprostol group ($n = 120$)	TA plus misoprostol group ($n = 120$)	p Value
Pulse (beats/min)	83.46 ± 7.5	90.99 ± 9.7	80.46 ± 4.97	.0001* .0001**/.003***/.0001****
Temperature (°C)	37.01 ± 0.07	37.45 ± 0.44	36.95 ± 0.13	.0001* .0001**/.1/.0001****
SBP (mmHg)	119.09 ± 3.67	113.04 ± 7.23	119.9 ± 2.18	.0001* .0001**/.193/.0001****
DBP (mmHg)	77.21 ± 4.29	73.04 ± 6.16	78.53 ± 2.66	.0001* .0001**/.026***/.0001****
Hemoglobin (gm/dl)	10.28 ± 0.81	9.08 ± 1.15	10.63 ± 0.78	.0001* .0001**/.004***/.0001****
Estimated blood loss (ml) median (range)	300 (250–950)	460 (350–1300)	290 (250–390)	.0001* .0001**/.043***/.0001****

TA: tranexamic acid; SBP: systolic blood pressure; DBP: diastolic blood pressure.
Variables are presented as mean and standard deviation.
*Statistical significant difference between all groups tested by ANOVA test.
**Statistical significant difference between oxytocin and misoprostol groups tested by Student's *t*-test.
***Statistical significant difference between oxytocin and TA plus misoprostol groups tested by Student's *t*-test.
****Statistical significant difference between misoprostol and TA plus misoprostol groups tested by Student's *t*-test.

both oxytocin group and TA plus misoprostol group ($p = .0001$).

There was a statistically significant lower hemoglobin level and higher blood loss in the misoprostol group compared with the oxytocin group and the TA plus misoprostol group ($p = .0001$). There was a statistically significant higher hemoglobin level and lower blood loss in the TA plus misoprostol group compared with the oxytocin group ($p = .004$ and .043, respectively) (Table 2).

The incidence of PPH was higher in the misoprostol group (16.7%) as compared with the oxytocin group (1.7%), while no cases of PPH in the TA plus misoprostol group ($p = .0001$). No significant difference in the incidence of PPH between the oxytocin group and the TA plus misoprostol group ($p = .498$), hence there was an increase in the use of additional uterotonics in the misoprostol group than both other groups. Blood transfusion was required in 13 women in the misoprostol group only.

There was increased incidence of nausea in the TA plus misoprostol group (11.7%) compared with the oxytocin group (1.7%) and the misoprostol group (2.5%) ($p = .002$ and .006, respectively). There were no significant differences between the three groups in the incidence of other side effects (Table 3).

Discussion

In the current study, prophylactic use of 1000 mg oral TA plus 600 μg buccal misoprostol during vaginal delivery effectively reduce the post-partum blood loss, blood transfusion needs as well as lower the incidence of PPH than misoprostol alone. Our study is the first one in evaluation of a novel combination of buccal misoprostol plus oral TA in the prevention of PPH. Adding TA to buccal misoprostol increases the efficacy of misoprostol in comparable with standard IV oxytocin. This combination can be very valuable in situations of unavailability of oxytocin or skilled birth-attendant during vaginal delivery as in cases of home birth which is prevalent in our country.

During delivery, when the placenta separates from the uterine wall, sequential physiologic, and

Table 3. The secondary outcomes of the study.

Outcomes	Oxytocin group ($n = 120$)	Misoprostol group ($n = 120$)	TA plus misoprostol group ($n = 120$)	p Value
Post-partum hemorrhage	2 (1.7)	20 (16.7)	0	.0001*
Additional uterotonics	2 (1.7)	20 (16.7)	0	.0001*
Need for blood transfusion	0	13 (10.8)	0	.0001*
Side effects Nausea	2 (1.7)	3 (2.5)	14 (11.7)	.001*
Vomiting	2 (1.7)	3 (2.5)	6 (5)	.339
Diarrhea	3 (2.5)	4 (3.3)	6 (5)	.683

All data are presented as number (percentage); TA: tranexamic acid.
*Statistical significant difference between all groups tested by Chi-square test.

hemostatic changes occur and reduce bleeding, including strong myometrial contractions, increased platelet activity, and a massive release of coagulation factors; at the same time, however, fibrinolytic activity increases [14]. While misoprostol administration enhances the first mechanism, TA administration might be able to counter the latter and thus facilitate the hemostatic process.

Our study reported a statistically significantly higher hemoglobin level and lower estimated blood loss in the TA plus misoprostol group compared with the oxytocin group ($p = .0004$ and .043, respectively) although this difference is not clinically relevant. Li et al. [15] conducted a meta-analysis to assess the efficacy and safety of TA in reducing blood loss and lowering transfusion needs for patients undergoing caesarean section (CS) or vaginal delivery (VD). They concluded that intravenous TA for patients undergoing CS was effective and safe. In addition, prophylactic TA administration is associated with reduced PPH [16].

Moreover, several studies evaluated the use of TA administration in VD [17,18] and showed satisfactory outcomes. Although published meta-analyses demonstrated that TA administration in CS or VD could result in a significant reduction in estimated blood loss, most of these studies are limited by the smaller samples and the poor quality of the included trials [19–21]. Moreover, data about clinical relevance of the reduced blood loss with TA intervention remained inadequate because these outcomes did not distinguish the efficacy of TA administration based on the mode of delivery.

A Cochrane systematic review published in 2010 identified two trials evaluating the TA administration in CS and VD [22]. Their study indicated that TA usage resulted in a significant reduction in total blood loss of 80.1 ml in CS and 71.5 ml in VD. Faraoni et al. [23] conducted a meta-analysis with 10 trials that evaluated the efficacy of TA administration in reducing blood loss for women undergoing CS or VD. They concluded that TA administration significantly reduced blood loss and lowered the occurrence rate of PPH regardless of the mode of delivery.

Gungorduk et al. [18] recruited 439 women with vaginal deliveries in a double-blinded RCT. Women in the intervention group received a single dose of 1.0 g of TA IV at delivery of the anterior shoulder, and those in the control group, a placebo. They reported significantly lower blood loss in the TA group than in the placebo group (261.5 ± 146.8 versus 349.98 ± 188.85 ml, $p < .001$). The incidence of PPH >500 ml was also lower in the TA group ($n = 4$, 1.8%) than in the control group ($n = 15$, 6.8%). Our results coincide with those studies.

A RCT conducted in Gambia compared 600 μg of oral misoprostol with 2 mg oral ergometrine. Although there was no difference in the PPH rate, there were fewer women with a fall in Hb >2 g/dl in the misoprostol group [24]. Additionally, a double-blinded RCT was carried out in a primary health center in Guinea-Bissau demonstrated a significant reduction in the rate of severe PPH (≥1000 ml) with 600 μg sublingual misoprostol [25]. Moreover, Derman et al. [26] in an Indian study reported that 600 μg oral misoprostol reduced the rate of severe PPH by 50% compared with placebo. The findings of these three trials show the effectiveness of misoprostol in low resource, community settings, where the PPH rate is very high and where there are no alternatives for prophylaxis or treatment.

A large multicenter trial of nearly 20,000 women comparing 600 μg of oral misoprostol with 10 IU of oxytocin showed that the rate of severe PPH (>1000 ml) was higher in the misoprostol group (4% versus 3%) [27]. A systematic review conducted for evaluation of the efficacy of misoprostol compared with placebo or other uterotonics in preventing maternal morbidity associated with the third stage of labor concluded that in less-developed countries, misoprostol represents a reasonable agent for the management of the third stage of labor [28].

There is a theoretical risk of thromboembolism with use of TA but our findings showed no thromboembolic events following TA administration. A study by Heesen et al. [21] evaluated the usage of TA in 1578 participants who undergoing CS or VD and

showed no associated between TA usage and any thromboembolic events. Our study showed that there was increased incidence of nausea in the TA plus misoprostol group (11.7%) compared with the oxytocin group (1.7%) and the misoprostol group (2.5%) ($p = .002$ and .006, respectively).

The strengths of our study include that it was a double-blinded, randomized, clinical trial with neither women nor the clinicians being aware of the group assignment. The study had its limitations. First, the small sample size of included women with the low incidence of occurrence of PPH among the study groups may limit the generalizability of our results. Additionally, we did not assess the use of intramuscular oxytocin for the prevention of PPH among study groups. Further studies with larger sample size are needed to confirm our results. Moreover, future studies should compare the use of oral TA versus the standard intramuscular oxytocin that used widely in low-resource settings.

In conclusion, adding TA may increase the efficacy of buccal misoprostol in preventing PPH. In settings like rural area or home delivery in which oxytocin is not available or its provision is not feasible, alternative buccal misoprostol plus TA may be considered for use.

Disclosure statement

The authors declare that they have no conflict of interest.

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