Sublingual Misoprostol and Intravenous Tranexamic Acid for Reducing Blood Loss during Elective Cesarean Section

Original Article

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ABSTRACT

Background: Obstetric blood loss is a significant cause of maternal mortality, and it is frequently underestimated and thus inadequately replaced. The most common major operation performed on women worldwide is a caesarean section. Cesarean section (C.S) is mainly linked to varying levels of blood loss.

Aim of the Work: Evaluate the effects of intravenous Tranexamic acid (TXA) and sublingual Misoprostol on reducing bleeding during C.S.

Materials and Methods: This was a prospective comparative study that was conducted at the obstetrics & gynecology department of Mansoura University Hospital and included one hundred patients with the following inclusion criteria: Elective CS, full-term birth (38-41 weeks), singleton pregnancy, and no medical disorders. Patients with severe medical and surgical conditions associated with pregnancy were excluded. Subjects included in the study were divided into two equal groups as follows: group A included 50 patients who received 400 µg sublingual misoprostol, and Group B included 50 patients who received 1 g Tranexamic acid. Follow up of vital signs, vaginal blood loss, and uterine tone every 30 minutes for 2 hours, then every hour up to 24 h. blood loss was calculated from the suction apparatus that collects blood after delivery of the placenta to exclude parietal blood loss and amniotic fluid, in addition to the surgical towels and mats below patients. A complete blood count was done before and 2 hours post-operative to calculate the haemoglobin and hematocrit deficit.

Results: Regarding the vital data, both systolic & diastolic blood pressure of Tranexamic acid were slightly lower than the misoprostol group either after delivery of the placenta or 2 hrs post-operative, but this difference was not statistically significant. Also, the post-operative heart beats were higher in the Tranexamic acid group than in the misoprostol group. The amount of sucked blood from Towels (Blood loss from placental delivery till end of operation) was higher in the Tranexamic Acid group (400.6 ± 37.8 ml) than misoprostol group (389.1 ± 45.7 ml). Also, the weight of the disposable mat (Blood loss from the end of operation till 24 h post-operative) in the Tranexamic Acid group was heavier than in the misoprostol group (641.3 ± 46.7 ml & 510.8 ± 58.8 ml respectively). The difference was statistically significant between both groups regarding the amount of sucked blood from Towels & the Weight of disposable mat (*P= 0.00 & 0.022* respectively).

Conclusion: Sublingual 400 µg of Misoprostol before elective cesarean section is a safe, easily administered medication that is associated with decreasing the incidence of PPH without causing complications.

Key Words: Decrease blood loss, sublingual misopristol, tranxamic acid.

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INTRODUCTION

Cesarean section is the delivery of a baby through an abdominal incision. Cesarean section (C.S) rates are increasing to as high as 25 to 30 % in many areas of the world[1].

Obstetric blood loss is a corner cause of maternal mortality and is consistently underestimated and consequently inadequately replaced[2]. Worldwide, caesarean section is the most common major surgery on women. Cesarean section is significantly associated with varying degrees of blood loss[3].

In many parts of the world, post-partum haemorrhage (PPH) is a leading cause of maternal loss and morbidity[4]. Post-partum haemorrhage accounts for nearly 25% of all maternal deaths, and of those who survive it, about 12% experience severe anaemia[5]. Although PPH-related mortality ratings have shown tremendous improvement over the past decade, the developing world still faces a disproportionate share of PPH and its effects[6].

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Despite all measures to prevent bleeding during and after C.S., post-partum haemorrhage (PPH) continues to be the most common complication seen in 20% of the cases, leading to increased maternal morbidity and mortality[7].

Therefore, practical preventive measures to lessen blood loss after caesarean sections should be implemented to reduce the likelihood of such problems.

Despite its effectiveness, Oxytocin is used worldwide to prevent uterine atony; 10-40% of women require additional uterotonic therapy, such as methyl ergometrine or 15-methyl prostaglandin F2α. Oxytocin should be stored between 4 and 8 □ C[8] to maximise efficacy.

Tranexamic acid (T.A.) treats haemorrhage, intra and post-operative blood loss, and other medical conditions[9].

Misoprostol may prevent PPH after vaginal or caesarean delivery instead of injectable uterotonics. Misoprostol may prevent PPH after vaginal or caesarean delivery instead of injectable uterotonics[10].

Misoprostol is cheap, easy to administer, tolerable, and has fewer side effects[11]. Also, TXA is a relatively inexpensive, safe drug available in most centres[12].

There is a lack of studies that compared the two drugs regarding their effectiveness in preventing post-partum haemorrhage following C.S. For this reason; the current study was conducted to evaluate the effects of intravenous Tranexamic acid and sublingual misoprostol on reducing bleeding during cesarean section.

PATIENTS AND METHODS

This prospective interventional study was conducted at the Obstetrics and Gynecology Department, Mansoura University Hospital, from July 2020 to October 2022.

The current study included 100 full-term birth singleton pregnancy patients who underwent elective C.S.

Cases with the following criteria were excluded: thyroid dysfunction, bleeding tendency, disseminated intravascular coagulopathy, acute liver or kidney disease, anaemia, allergy to Misoprostol or TXA, contraindications to misoprostol (bronchial asthma and heart disease), history of thromboembolic disorders, risk factors for PPH (such as polyhydramnios, fetal macrosomia, and antepartum hemorrhage, or prolonged obstructed labour), abnormal placenta (placenta previa and placental abruption), pregnancy induced hypertension, twins' pregnancy, BMI more than 30 and refusal to participate in the study.

The study follows the 2013 Helsinki Standards[13]. The institutional review board, Faculty of Medicine, Mansoura University, approved the study, and the included cases gave written informed consent.

Complete medical history and detailed physical examination were checked before the operation. Estimation of haemoglobin (Hb) levels and hematocrit (HCT) values. The change in Hb levels was calculated by comparing the 24-hour post-operative to preoperative Hb level. If Hb reduction was 1 gm/dl, it is considered massive blood loss.

While performing C.S., a small lower segment uterine incision of about 2 cm is made, followed by an opening of the amniotic sac to allow aspiration of amniotic fluid, and then C.S. is performed. This step is carried out to avoid miss calculation of the diluted blood with amniotic fluid as actual bleeding. As soon as the uterine incision was started, both groups delivered 20 units of Syntocinon. Delivery of the baby is carried out, then delivery of the placenta, and then the suction container is changed to exclude amniotic fluid and parietal blood loss.

The blood-stained pads used after delivery of the placenta are collected. During the first 24 hours after birth, unique mats (disposable mats ("INCO pads") of 90 x 60 cm were placed under buttocks, and the blood that spills from the uterus after birth was collected during cesarean and post-operative inpatient ward.

The weight of the gauze pieces, blood-stained pads used during the operation, and the weight of the mats used during the first 24 hours of operation are then weighted.

The following equation calculates the volume of lost blood: Blood loss volume = wet Weight of the pad or tampon - dry weight of the pad or tampon/1.05[14]. Follow up of vital signs, vaginal blood loss, and uterine tone every 30 minutes for 2 hours, then every hour up to 24 hrs.

Participants were divided into two equal categories as follows: Group A included 50 patients who received 400 mg sublingual Misoprostol (2 pills of Cytotec, 200 micrograms, Pfizer Inc.) administrated immediately before spinal anaesthesia and Group B included 50 patients who received 1 g TXA Slowly intravenously 5 ml ampoule (the equivalent of 1000 mg) of T.A. (Kapron, Amoun Pharmaceutical Co.) injected immediately before spinal anaesthesia.

Outcome Measures:

The primary outcome measure was the estimation of the amount of blood loss during and after cesarean delivery following administration of sublingual Misoprostol compared to intravenous TXA.

The secondary outcome measures are the need for blood transfusion, blood pressure changes, additional

ecbolic drugs, the changes in hematocrit and H.B. in both groups after delivery and the incidence of side effects.

Statistical analysis:

SPSS 26 for Windows® program was used to code, process, and analyse the data. Number (frequency) and percent qualitative data were presented. The Chi-Square (or Monte-Carlo) test compared groups. Kolmogorov-Smirnov tested quantitative data for normality. The data was presented as mean ± S.D. and range.

An independent samples t-test and Mann Whitney Test (U test) were used if the data were abnormally distributed. Spearman correlation correlated two sets of numeric data. *P values <0.05* are considered significant.

RESULTS

This study was conducted at Mansoura University on 100 elective cesarean section patients. It was approved by the institutional research board (IRB) of Mansoura Faculty of Medicine, the IRB no. MS.2210.5.

Table (1) shows no statistically significant differences between the two groups regarding patient's age, gravidity, parity, abortion, Gestational age or number of previous C.S.

Table 1: Clinical data of the studied groups

	Misoprostol group (n=50)		Tranexamic Acid group (n=50)		Independent t-test	
	Mean ± SD	Range	Mean ± SD	Range	t	*P*
Age (years)	29.6 ± 6.5	17-42	31.3 ± 6.5	18-45	- 1.300	*0.197*
BMI (Kg/m^2)	27.5 ± 1.4	24.2 – 29.4	27.4 ± 4.3	24.7 – 31.2	0.110	*0.912*
GA (weeks)	38.2 ± 0.8	38-41	37.8 ± 0.9	38-39	1.824	*0.052*
	Median	Range	Median	Range	Z	*P*
Gravidity (n)	3	(1-7)	3	(1-8)	- 1.144	*0.152*
Parity (n)	2	(0-4)	2	(0-5)	- 1.214	*0.136*
Abortion (n)	0	(0-4)	0	(0-4)	- 0.723	*0.215*
No previous C.S.	1	(0-4)	2	(0-5)	- 0.747	*0.455*

t: Independent t-test, Z: Mann-Whitney test

Table (2) shows no statistically significant difference between the two groups regarding Systolic, Diastolic, or Heart Rate for both preoperative and 2-hour post-operative measures.

Table 2: Hemodynamic parameters (Preoperative & Post-operative) for both groups

		Misoprostol group (n=50)		Tranexamic Acid group (n=50)		t-test	*P*
		Mean ± SD	Range	Mean ± SD	Range		
Blood pressure in mmHg	Systolic Bl. P (Preoperative)	117.9 ± 10.4	100-130	115.9 ± 9.6	95-135	1.63	*0.123*
	Diastolic Bl. P (Preoperative)	75.42 ± 7.2	60-90	75.3 ± 6.9	60-90	0.842	*0.257*
	Systolic Bl. P (2 h post-operative)	99.02 ± 10.5	90-120	100.0 ± 9.6	85-115	- 1.42	*0.081*
	Diastolic Bl. P (2 h post-operative)	66.1 ± 5.8	60-80	65.3 ± 6.2	60-85	0.69	*0.311*
Heart rate (beats/min)	Preoperative	83.7 ± 9.1	61-102	85.8 ± 5.9	75-108	- 1.52	*0.128*
	Two h post-operative	92 ± 9	72-101	92.4 ± 8.6	60-112	0.33	*0.665*

Table (3) shows the haemoglobin levels and hematocrit values for both groups (before & after delivery). Seven cases that needed blood transfusion were excluded (4 in the Tranexamic Acid group & 3 in the misoprostol group). Although the deficit in H.B. and H.T. values in the Tranexamic Acid group was higher than the misoprostol group, the difference was statistically insignificant.

Table 3: Hemoglobin & hematocrit values (Preoperative & Post-operative) for both groups (before & after delivery)

	Misoprostol group (n= 47)		Tranexamic Acid group (n=46)		t- test	*P*
	Mean ± SD	Range	Mean ± SD	Range		
HB (gm/100 ml) before delivery	11.1 ± 0.9	9.9-13.9	11 ± 1.9	9.9-11.9	0.32	*0.412*
HB (gm/100 ml) after delivery	10.4 ± 0.9	8.9-13.1	10.5 ± 0.9	8.2-10.4	- 0.593	*0.555*
HB (gm/100 ml) deficit	0.8 ± 0.4	0.1-1.7	1.1 ± 0.5	0.4-2.7	1.53	*0.08*
HT % before delivery	33.7 ± 2.7	26.4-38.1	33.4 ± 2.4	30.1-36.5	0.471	*0.639*
HT % after delivery	32.8 ± 1.9	24.3-35.5	32.5 ± 2.1	28.1-33.2	0.876	*0.383*
HT % deficit	1.1 ± 0.7	0.1-3.2	1.9 ± 0.8	0.5-3.9	0.62	*0.211*

HB = Hemoglobin, HT = Hematocrit
* P value is statistically significant at level < *0.05*
N.B: cases that need blood transfusion were excluded

In Table 4, the amount of sucked blood from Towels & the Weight of disposable mat were higher in the Tranexamic Acid group than misoprostol group & there is a statistically significant difference between both groups regarding total blood loss (*P= 0.001*). The total number of cases who needed blood transfusion was higher in the Tranexamic Acid group (4 patients) than in the misoprostol group (3 patients), as the number of transfused units was higher in the Tranexamic Acid group (8 units) than misoprostol group (5 units).

Table 4: Amount of blood loss for both groups

		Misoprostol group (n= 50)		Tranexamic Acid group (n=50)		T	*P*
		Range	Mean ± SD	Range	Mean ± SD		
Intraoperative	Amount of blood in suction (in ml)	100 - 208	152.5 ± 33.9	110 - 233	159.9 ± 33.7	- 1.09	*0.27*
	Weight of Towels sucked with blood in grams (A)	197.0 - 384.2	274.17 ± 34.1	257- 534.6	314.2 ± 47.3	- 4.85	*0.001**
	Amount of blood in Towels (in ml) (A)	168.57 - 287.9	236.5 ± 24.7	240.5 - 286.7	240.8 ± 26.5	- 0.84	*0.40*
	Blood loss in ml (A)	268.57 -495.9	389.1 ± 45.7	250.5 -519.7	400.6 ± 37.8	- 1.37	*0.17*
Post-Operative	Weight of disposable mat in grams (B)	105 - 130	117.16 ± 7.68	122 - 205	167.7 ± 23.9	- 14.2	*0.001**
	Post-operative blood loss in ml (B)	76.19 - 171.4	121.7 ± 33.04	149.5 - 286.7	240.8 ± 26.5	- 19.8	*0.001**
Total blood loss in ml		344.67 -667. 3	510.8 ± 58.8	399 -805.4	641.3 ± 46.7	- 12.28	*0.001**

(A) Blood loss from placental delivery till the end of the operation
(B) Blood loss from end of operation till 24 hrs post-operative
* Statistically significant at *P< 0.05*

In seven cases, blood transfusion was required, three in the misoprostol group and four in the Tranexamic Acid group. The amount of sucked blood from towels, the weight of the disposable mat, and total blood loss were higher in the Tranexamic Acid group than in the misoprostol group. Still, these differences were statistically significant, with a *p-value* of *0.001* In (Table 4).

Table (5) shows that in the misoprostol group, the number of abortions and increased orders of C.S. have the most remarkable significant positive correlation with blood loss, outweighing all other parameters in the Tranexamic Acid group. The increased order of parity and number of abortions have the most remarkable significant positive correlation with blood loss, outweighing all other parameters.

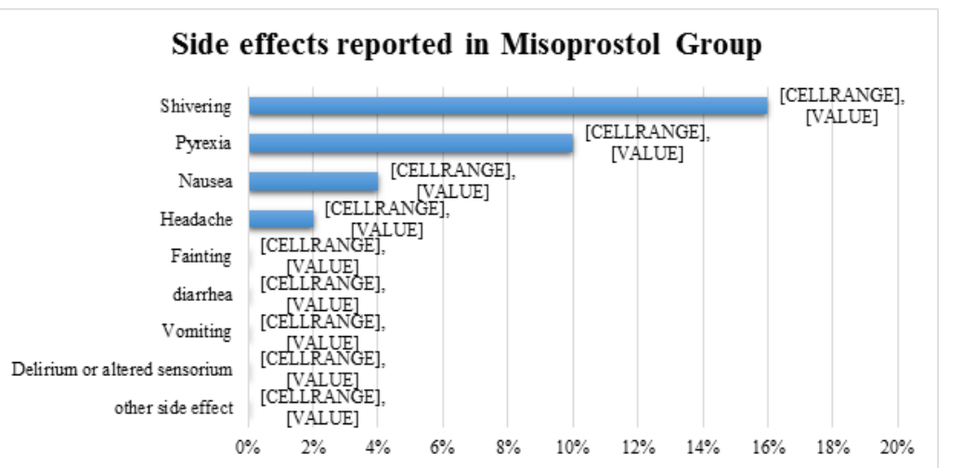
Table 5: Influence of prenatal clinical data on total blood loss in the misoprostol group

	Misoprostol group		Tranexamic Acid group	
	Correlation Coefficient	Significance	Correlation Coefficient	Significance
Maternal age (years)	0.094	0.232	0.242	0.052
Gravidity (n)	0.033	0.107	0.143	0.124
Parity (n)	0.209	0.109	0.281	0.05*
Abortion (n)	0.274	0.042*	0.299	0.032*
G.A. (weeks)	0.036	0.112	0.089	0.306
No. of C.S. (n)	0.334	0.003*	0.023	0.273

GA= Gestational age , CS= Cesarean section ,
* Statistically significant at *P< 0.05*

The most common side effects reported in patients who received Misoprostol were shivering (8 cases, 16%), pyrexia (5 cases, 10%), nausea (2 cases, 4%), and headache (1 case, 2 %). The most common side effects reported in patients who received tranexamic acid were headache (3 cases, 6 %), nausea (2 cases, 4 %), vomiting (1 case, 2 %), runny or stuffy nose (1 case, 2 %), stomach pain or discomfort (1 case, 2 %), and dizziness (1 case, 2 %).

Fig. 1: Side effects reported in both groups



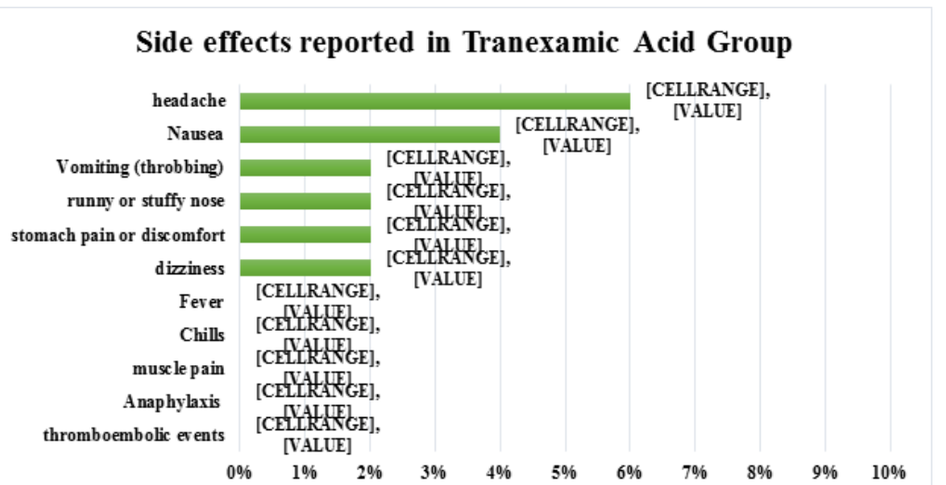


Table (6) shows the number of cases that required additional ecbolic drugs due to uterine atony. The total number of cases was higher in the Tranexamic Acid Group (8 cases, 16 %) than in the Misoprostol Group (5 cases, 10 %).

Table 6: Cases needed additional ecbolic drugs

	Misoprostol Group (n=50)		Tranexamic Acid Group (n=50)	
	N	%	N	%
Total	5	10.0%	8	16.0%
10 units Syntocinon	2	4.0%	3	6.0%
20 units Syntocinon	1	2.0%	2	4.0%
40 units Syntocinon	1	2.0%	1	2.0%
100 mg Carbetocin	0	0.0%	1	2.0%
400 mg misoprostol	1	2.0%	1	2.0%
0.5 mg Ergometrine	0	0.0%	0	0.0%

DISCUSSION

This study aimed to decrease intraoperative and post-operative blood loss during C.S. Uterotonic drugs necessitate expert administration and have adverse effects at therapeutically adequate levels; Misoprostol is a simple agent and can be given oral, sublingual, rectal, vaginal and even intrauterine.

The following variables were comparable between the two groups: age, gravidity, parity, abortion, gestational age and number of previous C.S. Moreover, SBP, DBP and H.R. (preoperative and 2-hour post-operative measures) revealed similar attitudes.

In agreement with the current results, Safi *et al*. (2021) studied 146 pregnant women who did C.S. Two groups were formed from all patients. Groups I and II included 73 participants and received sublingual Misoprostol (600 µg) and 500 mg intravenous tranexamic during cord clamping. In the TXA group, the mean arterial pressure (MAP) was statistically lower, and the mean H.R. was more[15]. The intravenous tranexamic lowered haemoglobin levels more than sublingual Misoprostol.

The results also agree with Pakniat *et al*., who categorise 158-term C.S. into two groups. In the misoprostol group, two 400 µg sublingual pills were given immediately after delivery. T.A. ampoule (1 g) was injected 10 minutes before the skin incision in the TXA group. They found that the T.A. group had considerably lower mean blood pressure throughout the operation than the M group ($P < 0.001$).[16]

In the current study, the deficit in H.B. and H.T. values in the Tranexamic Acid group was higher than in the misoprostol group; the difference was statistically insignificant. Tabatabaie *et al*., 2021, found a significant difference in haemoglobin scores before surgery between Tranexamic acid, Misoprostol, and placebo groups, with mean scores of 11.96±1, 11.62±1.21, and 12.28±1.26 gm/dl, respectively (*P=0.001*). Post-operative haemoglobin levels decreased by 1.02±0.35 (10.9±0.99 gm/dl) in Tranexamic acid, 1.19±0.52 (10.46±1.04 gm/dl) in Misoprostol, and 1.36±0.50 (10.93±1.34 gm/dl) in placebo[17].

In the current study, the mean amount of post-operative blood loss in the misoprostol group was 121.7 ± 33.04 ml, which was statistically significantly lower as compared to the post-operative amount of blood loss in the TXA group (240.8 ± 26.5 ml) ($p= 0.001$). Moreover, the weight of towels sucked with blood in grams was heavier in the TXA group during the intraoperative and post-operative periods.

The study of Bose and Beegum (2012) showed that the TXA group had a statistically negligible reduction in blood loss compared to the misoprostol group, regardless of high-risk characteristics (470.30 vs 491.74 mL, $p = 0.487$)[18].

Also, in contrast to the current study, Sahhaf *et al*. reported that haemoglobin levels and bleeding volume were comparable between the two drugs (Misoprostol and intravenous T.A.) during follow-up of 6 to 12 hours[19].

In the current study, complications were somewhat higher in the misoprostol group. The most common side effects reported in patients who received Misoprostol were shivering (8 cases, 16%), pyrexia (5 cases, 10%), nausea (2 cases, 4%), and headache (1 case, 2 %). The most common side effects reported in patients who received tranexamic acid were headache (3 cases, 6 %), nausea (2 cases, 4 %), vomiting (1 case, 2 %), runny or stuffy nose (1 case, 2 %), gastric pain or discomfort (1 case, 2 %), and dizziness (1 case, 2 %). Pakniat *et al*. agreed with us and showed that adverse events, including diarrhoea, vomiting, nausea, fever, hysterectomy, or blood transfusion, were comparable between the two groups[16].

In the current study, the total number of cases that required additional ecbolic drugs due to uterine atony was higher in the Tranexamic Acid Group (8 cases, 16 %) than in the Misoprostol Group (5 cases, 10 %). Still, it didn't reach a statistically significant level.

CONCLUSION

Sublingual 400 µg of Misoprostol given immediately before spinal anaesthesia effectively reduced blood loss during and after caesarean sections and prevented post-partum haemorrhage, which is still the leading cause of maternal death worldwide. Total bleeding was significantly lower in sublingual Misoprostol than in the tranexamic acid group. Furthermore, in the Misoprostol group, hemodynamic variables were stabilised more than in the tranexamic acid group.

RECOMMENDATIONS

In suspected cases of placenta accrete by ultrasound, We recommend to evaluate every change in CBC parameters which can predict placental invasion anomalies eg. Mean platelet Volume(MPV), Neutrophil / lymphocyte (N/L) ratio and Red cell Distribution Width (RDW), Platelet's count.

CONFLICT OF INTEREST

There are no conflicts of interests.

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