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Original article

Rectal misoprostol versus tranexamic acid for reducing intra &post-operative blood loss in cesarean section

Ashraf Samir Faheem[1], Mohamed Ragab Gomaa[1] , Reham S. Alfakharany[2], Ahmed A. Taha[1]

[1] *Obstetrics and Gynecology department, Faculty of Medicine, Beni-Suef University, Egypt*

[2] *Physiology Department, Faculty of Medicine, Beni-Suef University, Beni-suef, Egypt*

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Corresponding Author:

Mohamed Ragab Gomaa

ali20285@gmail.com

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Abstract:

Objective: Aim: To assess the impact of intravenous tranexamic acid (TA) and rectal misoprostol on reducing blood loss during and after cesarean section in low and high-risk groups. **Methodology**: The study involved 200 pregnant women scheduled for elective cesarean delivery at Beni-Suef University hospital. Participants were randomly divided into two main groups: high-risk and low-risk. Each group was further split into two subgroups: one receiving 400 microgram rectal misoprostol and the other receiving 1 gm (10 ml) (2amp) intravenous tranexamic acid. Post-delivery, all patients received a 10 IU oxytocin (Syntocinon) intravenous bolus. Additional ecbolics (10 IU oxytocin and IM ergometrin) were administered only if blood loss exceeded 500ml or at the surgeon's request. Blood loss was measured post-surgery by weighing pads and monitoring loss during the first 24 hours.

Results and Conclusion: Both rectal misoprostol and intravenous tranexamic acid demonstrated comparable effectiveness in reducing blood loss during and after cesarean delivery in both low and high-risk patients for postpartum hemorrhage (PPH). No statistically significant differences were observed among the studied groups regarding the occurrence of postpartum hemorrhage (>1000ml in the first 24 hours) or the neonate's Apgar scores at 1 and 5 minutes. Neither misoprostol nor tranexamic acid side effects were reported.

1. Introduction:

Cesarean section stands as the most prevalent major surgical procedure for women globally. The past two decades have witnessed a continuous rise in cesarean delivery rates, with Egypt ranking among the countries with the highest incidence {1}.

Post-partum hemorrhage (PPH) continues to be the leading cause of maternal deaths in developing countries. The increasing prevalence of cesarean sections has been recognized as the principal contributor to PPH {2}.

PPH is characterized by blood loss exceeding 1000 ml during a cesarean delivery. Various factors can lead to post-partum hemorrhage, including uterine atony, genital tract trauma, and retained placental tissue {3}.

As cesarean section rates and associated complications increase, there is growing concern about the inadequate management of severe bleeding during and after the procedure {4}.

Uterotonic agents, primarily oxytocin, are commonly employed to reduce cesarean-related hemorrhage {5}. However, research indicates that oxytocin administration may lead to adverse maternal effects such as hypotension and tachycardia {6}.

Consequently, there is a need for therapeutic agents with enhanced efficacy and fewer side effects. Recent studies have revealed a link between fibrinogen and cesarean-related hemorrhage. Additionally, extensive tissue injury can increase fibrinolysis, resulting in bleeding {7}.

Anti-fibrinolytic agents, like tranexamic acid (TA), can potentially decrease bleeding risk.

Studies have concluded that tranexamic administration can reduce blood loss and the occurrence of postpartum hemorrhage following elective cesarean sections {8}.

Misoprostol, a prostaglandin E1 analogue, has been introduced as a uterotonic agent to mitigate the risk of PPH after cesarean sections. A recent study determined that misoprostol is more effective than placebo in reducing major PPH following cesarean delivery {9}.

Misoprostol can be administered through various routes: oral, sublingual, vaginal, rectal, and intrauterine. The drug's pharmacokinetics does not clearly indicate its exact onset of action. As an example, the effectiveness of misoprostol when administered vaginally is affected by the vagina's acidic environment and bacterial composition {10}.

2. Subjects and Methods:

2.1. patients:

A randomized cohort study was performed on 200 pregnant women attending for elective CS at Beni-Suef University hospital's Department of Obstetrics and Gynecology between November 2021 and July 2022. This study was approved by the Ethical committee of faculty of medicine Beni-suef university (Approval No: FMBSUREC/01112021/Gomaa) complied with the Declaration of Helsinki principles. Written informed consent was obtained from all patients.

Pregnant women candidate for elective LSCS with gestational age >38w (confirmed by the 1st day of the LMP or 1st trimester ultrasound scan), Age: 20-40 years old.

(For high risk group only)Cases with high risk for Atonic Post partum hemorrhage as:. {Multiple pregnancies,polyhydraminos,large baby>4kg (overdistended uterus)}

, Cases with history of atonic PPH.

Exclusion of the patients was based on the following (for both groups) Fetal death ,Prolonged procedure , History of prostaglandin or Tranexamic acid allergy,CS under general anesthesia,Maternal medical disorder,Placenta previa,Placental abruption.(For Low risk Groups only)

Cases with high risk for Atonic Post partum hemorrhage.

All participants were subjected to informed written consent, full medical history, clinical examination, obstetric ultrasonography, preoperative routine tests(CBC,PT,PC,INR,virology,LFT,KFT).The participants were randomly allocated to two groups First group is high risk group ,second group is low risk group ,then each group is subdivided into 2groups one of them is misoprostol group and the other is

tranexamic acid group .In each Tranexamic acid group , patients were given 1 gm(10 ml)(2amp) Tranexamic acid (Kapron, Amoun, Egypt)diluted in 20 ml of Glucose 5% (administered IV slowly over 5 minutes, at least 15 minutes prior to skin incision).In each Misoprostol group , 400 microgram misoprostol (2 tablets - Cytotec, Pfizer, G.D. Searle LLC) were administered rectally by doctor other than the operating obstetrician after insertion of Foley catheter and shortly before skin incision . Following delivery of the baby's shoulder, All patients additionally received an intravenous bolus of 10 IU oxytocin (Syntocinon, Novartis,Basel, Switzerland) & additional ecbolics(in form of 10 IU oxytocin & IM ergometrin) only if blood loss exceed 500ml or on demand of the operating surgeon. The time interval between drug administration and fetal delivery was recorded together with the neonatal outcome.

2.2. Statistical Analysis:

Statistical reporting of data will include range, mean, standard deviation (±SD), median, and frequencies (both in number of cases and percentages) as appropriate. To compare quantitative variables between groups, the Student t test for independent samples will be employed. Chi square (χ 2) tests will be used for categorical data comparisons, with Yates correction applied when expected frequencies fall below 5. Statistical significance will be determined by a probability value (p value) less than 0.05. All statistical analyses will be conducted using Microsoft Excel version 7 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) software programs.

3. Results:

Group I: High risk Misoprostol

Group II: Low risk Misoprostol

Group III: High risk TXA

Group IV: Low risk TXA

Table (1) Maternal baseline characteristics of the studied patients:

Items	Group I (No=50)	Group II (No=50)	Group III (No=50)	Group VI (No=50)	P-value
Maternal age(y)	24.6±3.8	23.6±1.9	23.8±2.7	24.7±2.2	0.153
Maternal BMI	22.5±2.2	22.7±1.8	23.3±2.3	23.4±1.6	0.077
GA of termination(w)	38.3±0.6	38.9±0.7	38.3±0.6	38.6±0.8	---
Number of CS [median (IQR)]	1(0,1)	1(0,2)	1(0,2)	1(0,2)	0.220

This table showed that there was no significant difference regarding maternal baseline characteristics of the studied groups (P-value >0.05).

Table (2) Follow up blood pressure and pulse from pre-operative to postoperative in the studied patients:

Items	Group I (No=50)	Group II (No=50)	Group III (No=50)	Group VI (No=50)	P-value
Pre-operative SBP	114.6±6.8a	119±8.6b	112.4±4.3a	119.8±8.4b	<0.001*
Post-operative SBP	102±6.1a	106.8±7.4b	100.8±5.3a	107.9±7.6b	<0.001*
P-value pre vs post	<0.001*	<0.001*	<0.001*	<0.001*	
Pre-operative DBP	69.8±1.4	69.8±1.4	69.8±1.4	69.8±1.4	>0.999
Post-operative DBP	69±3	69.8±1.4	68.6±3.5	69.6±1.9	0.088
P-value pre vs post	0.044*	<0.001*	0.032*	0.569	
Pre-operative Pulse	82.3±3.4	81.4±2.6	81.5±2.3	82.1±2.2	0.273
Post-operative Pulse	89.6±5.2	87.4±4.1	88.5±4.9	88.4±3.9	0.140
P-value pre vs post	<0.001*	<0.001*	<0.001*	<0.001*	

**P-value is significant*

N:B: different colored letters indicate significant difference between groups.This table showed that there was no significant difference in pre and postoperative diastolic blood pressure and pulse (P-value >0.05) but, the pre-operative and post-operative systolic blood pressure was statistically higher in group II and group IV than group I and III (P-value <0.001).

Table (3) Follow up hemoglobin and hematocrit from pre-operative to postoperative in the studied patients:

Items	Group I (No=50)	Group II (No=50)	Group III (No=50)	Group VI (No=50)	P-value
Pre-operative HB	11.3±0.5	11.4±0.7	11.5±0.5	11.6±0.7	0.187
Post-operative HB	10.2±0.7	10.3±0.8	10.4±0.7	10.6±0.8	0.054
P-value pre vs post	<0.001*	<0.001*	<0.001*	<0.001*	
Pre-operative HCT	34±1.4	33.9±2.2	34.4±1.7	34.5±2	0.400
Post-operative HCT	30.6±2.1	30.6±2.3	31.4±2.2	31.3±2.2	0.165
P-value pre vs post	<0.001*	<0.001*	<0.001*	<0.001*	

**P-value is significant*

N:B: different letters indicate significant difference between groups.This table demonstrated no significant statistical difference between the studied groups regarding pre and postoperative hemoglobin and hematocrit value (P-value >0.05) they significantly decreased after the operation in each group (P-value <0.05).

Figure (1) Pre and post operative hemoglobin

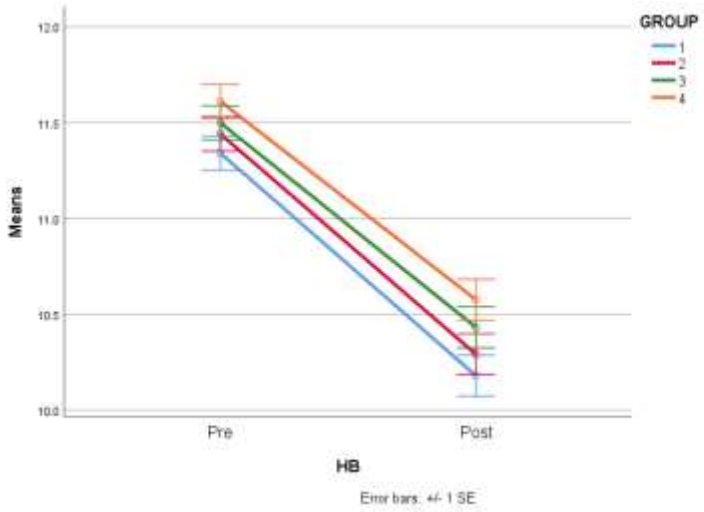

Table (4) Blood loss in the studied patients:

Items	Group I (No=50)	Group II (No=50)	Group III (No=50)	Group VI (No=50)	P-value
Intraoperative used towels	5.8±0.8a	4.9±0.6b	6.2±0.9c	4.8±0.8b	<0.001*
Postoperative used towels	1±0.1	1.1±0.4	1.3±0.9	1.1±0.4	0.154
Difference in weight of towels intraoperative(gm)	403.2±59.3a	340.2±40b	432.6±59.5c	332.4±55.1d	<0.001*
difference in weightof towels postoperative(gm)	71.4±9.8	75.6±31.1	88.2±62.9	96.4±100.	0.158
EBL (ml)	583.6±81.2a	516.8±72.3b	647±110.9c	529±109.4b	<0.001*
Blood in suction(ml)	109±26.1a	101±34.2a	126±55.5b	115±56.4a	0.045*

**P-value is significant*

N:B: different colored letters refer to significant difference between groups.This table showed that there the intraoperative used towels, difference of weight of towels and EBL were statistically lower in group II and group IV than group I and III (P-value <0.001). Blood amount in suction was significantly more in group III than the other three groups.

Table (5) Post operative complications in the studied patients:

Items	Group I (No=50)	Group II (No=50)	Group III (No=50)	Group VI (No=50)	P-value
Atonic PPH in 1st 24 hours	5(10.0%)	2(4.0%)	8(16.0%)	4(8.0%)	0.225
SE of misoprostol or TXA	0(0%)	0(0%)	0(0%)	0(0%)	---
Need to ecbolic	5(10.0%)	2(4.0%)	8(16.0%)	4(8.0%)	0.225

This table demonstrates no significant difference between the occurrence of atonic postoperative, side effects of the administered drugs and need to ecbolic (P-value >0.05)

Table (6) Neonatal outcomes in the studied patients:

Items	Group I (No=50)	Group II (No=50)	Group III (No=50)	Group VI (No=50)	P-value
APGAR 1st min	6.6±0.5	6.6±0.6	6.5±0.7	6.6±0.6	0.667
APGAR 5th min	9.6±0.5a	9.6±0.5a	9.3±0.8b	9.5±0.5a	0.010*
Neonatal weight	3.9±0.7a	3.4±0.3b	4.3±1.1c	3.3±0.3b	<0.001*
Need NICU	0(0%)	0(0%)	0(0%)	0(0%)	---

This table showed significant lower APGAR score and higher neonatal weight in group III than the rest three groups (P-value<0.05).

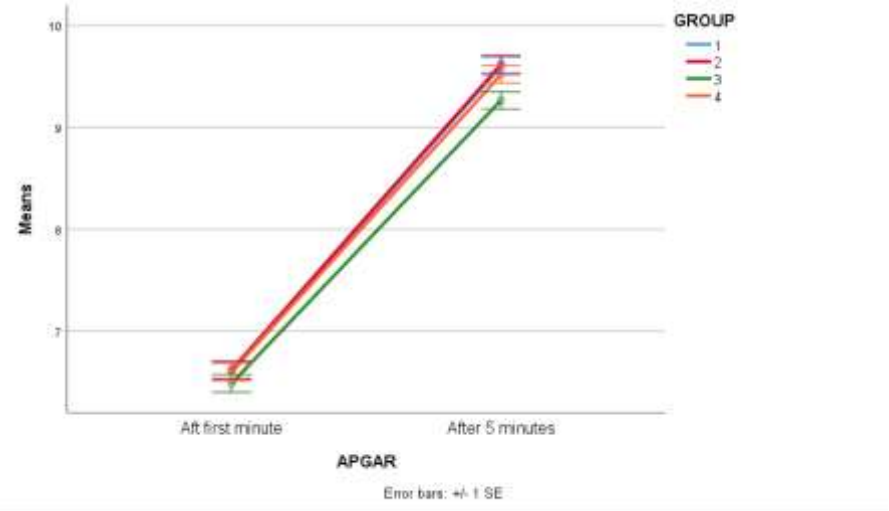

Figure (2) APGAR score after 1st and 5th minutes

4- Discussion:

This randomized cohort study aims to evaluate the effectiveness and safety of administering Tranexamic acid intravenously and Misoprostol rectally before surgery to reduce blood loss during and after cesarean sections in both high-risk and low-risk pregnancies.

Our findings indicate that both rectal misoprostol and intravenous Tranexamic acid are similarly effective in minimizing blood loss during and after cesarean deliveries for patients at low or high risk of postpartum hemorrhage (PPH). Additionally, no statistically significant differences were

observed between the groups regarding postpartum hemorrhage (exceeding 1000ml within 24 hours) or the newborn's Apgar scores at 1 and 5 minutes. No adverse effects from misoprostol or tranexamic acid were reported.

Corroborating our results on TXA's efficacy in reducing intraoperative and postoperative blood loss, Halder etal (2013), sahu etal, and Mishra etal(2019) found that tranexamic acid effectively decreases bleeding without associated complications such as venous thromboembolism, gastrointestinal discomfort, or hypersensitivity{11}{12}.

These studies reported significantly lower mean intra-operative and post-partum blood loss in the study group compared to the control group:Halder et al (2013) noted a significantly better hemoglobin drop in the study group (1.214 g/dl) versus the control group (1.7256 g/dl) ($p < 0.0001$).

According to sahu etal and Mishra etal(2019), the mean blood loss (intra and postoperative) was 436.5 ± 118.07 mL in the study group compared to 616.5 ± 153.34 mL in the control group ($P \leq 0.05$). Only two (4%) patients in the study group experienced blood loss >500 mL during cesarean section, compared to nine (18%) in the control group ($P \leq 0.05$). The postoperative mean change in hemoglobin was 0.494 ± 0.12 g % and 0.594 ± 0.16 g % ($P \leq 0.05$) in the study and control groups, respectively.

These studies conclude that TXA is an affordable antifibrinolytic drug that significantly reduces intra and postoperative bleeding in cesarean sections, making it particularly valuable in resource-limited settings.

However, these studies differ from our research primarily in the timing of TXA administration. In their studies, TXA was administered immediately before skin incision and compared with a placebo, whereas in our study, TXA was given 15 minutes before skin incision and compared with misoprostol.

In contrast to our results, the study by Sherafati et al. (2017) did not detect any alterations in blood loss following placental delivery {13}.Their study found no notable differences in vaginal bleeding volume within 6 hours post-surgery, vital signs (blood pressure and pulse rate), or blood profile (hemoglobin, hematocrit, and platelet count) between patients who received tranexamic acid during CS and those who did not. The study involved 65 women scheduled for CS, randomly assigned to a case group (n=32) receiving 1 g of tranexamic acid during anesthesia and 30 u of intravenous

oxytocin after placenta delivery, and a control group (n=33) receiving only 30 u of intravenous oxytocin post-placenta delivery. Blood loss was assessed by counting bloody sponges (15 cc each) and post-surgery pads, with total bleeding measured in the first six hours. Blood parameters were measured pre-surgery, 2 hours, and 24 hours post-CS. The researchers reported no significant inter-group differences in bloody sponge count, suction blood volume, total bleeding, post-placental delivery bleeding (p=0=372), vaginal blood loss within six hours (p=0.827), total blood loss within six hours (p=0.382), hemoglobin levels (pre-surgery p=0.242; 2 hours post-surgery p=0.55; 24 hours post-surgery p=0.98), hematocrit levels (pre-surgery p=0.156; 2 hours post-surgery p=0.623; 24 hours post-surgery p=0.622), and platelet count (pre-surgery p=0.156; 2 hours post-surgery p=0.457; 24 hours post-surgery p=0.883). They concluded that intravenous tranexamic acid during CS does not significantly reduce post-CS blood loss. Our current study differs in sample size, timing of tranexamic acid administration, methods for estimating intraoperative blood loss, and uses a higher oxytocin dose.. Christian O. Ogah et al. (2022) (14) conducted a randomized controlled study at Alex Ekwueme Federal University Teaching Hospital, Abakaliki, Nigeria, employing a methodology comparable to this investigation. The study involved 514 pregnant women scheduled for cesarean section, randomly divided into two groups of 257 patients each. One group received 1000 µg of rectal misoprostol preoperatively, while the other was administered 1000mg of intravenous tranexamic acid following spinal anesthesia. Sixteen participants were excluded from the analysis: nine due to incomplete proformas and seven lost to follow-up.

The study found no significant difference in mean intraoperative bleeding between the misoprostol and tranexamic acid groups (547 ± 183.75ml vs. 551.66 ± 21.74ml, P = 0.157). Similarly, the mean difference in pack cell volume (PCV) was not statistically significant between the groups (2.41±0.95% vs. 2.36±0.56%, P = 0.474). Adverse effects were comparable for both groups, except for shivering, which was more prevalent in the misoprostol group (RR = 0.70; 95%CI 0.40 - 0.91, P = 0.028).

The researchers concluded that intravenous tranexamic acid was as effective as rectal misoprostol in reducing blood loss during cesarean section. They suggested that tranexamic acid could be considered a suitable alternative to misoprostol for

prophylaxis of blood loss during elective cesarean section.

The current study utilized higher doses of misoprostol and tranexamic acid and compared their effects regardless of the risk of intraoperative or postoperative bleeding.

5. Conclusion:

The research found that rectal misoprostol and intravenous tranexamic acid were equally successful in reducing blood loss during and after cesarean sections. This effectiveness was observed regardless of whether patients were at low or high risk for postpartum hemorrhage.

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Ethics declarations

The study was conducted after receiving approval from the Ethics Committee of the Institutional Review Board at Beni-Suef University's faculty of medicine. The study's approval number was (Approval No: FMBSUREC/01112021/Gomaa). All participants were informed about the study's objectives and provided informed consent before taking part. Throughout the research, data confidentiality was maintained.

Competing interests

The researchers declare no conflicts of interest.

Data access: The original data for this research was gathered at the Obstetrics & Gynecology Department within the Faculty of Medicine at Beni-Suef University. Researchers seeking access to the data that supports this study's conclusions can reach out to the corresponding author.

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