Intravenous tranexamic acid vs. sublingual misoprostol in high-risk women for postpartum haemorrhage following cesarean delivery; a randomised clinical trial

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Introduction

- The cesarean section (CS) rate is still sharply growing, as CS is the commonest major obstetric procedure performed worldwide.

- Despite the advances in the medical field, obstetric hemorrhage remains a well recognized complication of childbirth in both developed and developing countries.

- Obstetric hemorrhage is identified as the second leading cause of maternal mortality in developed countries while considered the primary cause of maternal mortality in developing countries.

- Postpartum hemorrhage (PPH), either primary or secondary, is considered one of the commonest types of obstetric hemorrhage.

- In 2017, the American College of Obstetrics and Gynecology updated the definition of primary PPH to be a cumulative blood loss higher than 1000 mL with clinical features of hypovolemia within 24 h of birth, regardless of the delivery route.

- Uterine atony, lacerations, retained tissues or blood clots and coagulation factor deficiencies are the most common causes of PPH.

- Management strategies include uterine massage, oxytocin, methylergometrine, and circulatory support with or without blood transfusion. It has been estimated that about 5% of cesarean delivery may experience PPH.

- Since prevention of PPH is the cornerstone of management, the National Collaborating Centre for Women's and Children's Health has recommended the administration of intravenous 5 IU of oxytocin routinely following the cesarean delivery as a prophylactic measure against PPH.

- Misoprostol, a prostaglandin E1 analogue, has been introduced as a uterotonic agent to prevent PPH after CS.

- A Cochrane review has concluded that the combination of misoprostol and oxytocin was one of the most effective combinations in reducing blood loss compared to oxytocin alone.

- Tranexamic acid is an antifibrinolytic medication that acts by blocking lysine binding sites on plasminogen molecules.

- Several studies have addressed its use in preventing PPH following CS and showed the effectiveness of tranexamic acid when added to oxytocin in preventing blood loss.

- A Cochrane review has also shown its effectiveness when used alone in a dose of 0.5-1 gm intravenously in low-risk women for PPH.

Aim of the study

- Our study aimed to reach the most effective protocol in reducing intra and post-operative blood loss in high-risk women for PPH following CS.

- Therefore, we compared the effectiveness of the combined use of sublingual misoprostol and IV oxytocin with that of the combined use of IV tranexamic acid and oxytocin. Also, we compared them with the effectiveness of oxytocin when given alone.

Methods

- A randomized clinical trial was carried out, following the CONSORT guidelines, in Kasr Al-Ainy Hospital (Obstetrics and Gynecology Department, Faculty of Medicine, Cairo University) from January 2020 to December 2020 after approval of the Medical Ethical Committee.

- This clinical trial was registered at www.clinicaltrials.gov on 07/10/2019 with registration number NCT04117243.

- The study included 345 pregnant women who were candidates for lower segment cesarean section (LSCS) under spinal anaesthesia.

Inclusion criteria

- Maternal age 20–40 years
- Term pregnancy (≥37 weeks), with one or more of the high risk for PPH criteria ; like

(1) Maternal anemia (Hb< 9.9 g%)

(2) Chronic maternal medical disorders (e.g., cardiac, renal, DM)

(3) Preeclampsia or gestational hypertension

(4) Macrosomia

(5) High-risk cases for obstetric haemorrhage

Exclusion criteria

(1) Intrauterine fetal death (IUFD)

(2) Fetal anomalies or growth retardation (FGR)

(3) Emergency CS

(4) More than two previous CS procedures

(5) Prolonged procedure (more than two hours from skin incision to skin closure)

(6) Abnormally invasive placenta

(7) Known or history of thromboembolic events

(8) History of prostaglandin or Tranexamic acid allergy.

- All participants underwent the following steps to confirm their eligibility for this study:

  (1) full medical and obstetric history

  (2) general and obstetric examination

  (3) obstetric ultrasound

  (4) pre-operative laboratory tests: including complete blood count (CBC), coagulation profile, and liver and kidney function tests.

- On the day of the scheduled surgery, the participants were randomly assigned into three groups; Tranexamic Group, Misoprostol Group, and Oxytocin-only Group (as a control group). Randomization was performed using computer-generated random numbers.

- In the tranexamic group, 1 gm (10 ml) of tranexamic acid was diluted in 20 ml of Glucose 5%, then given to the patients as an intravenous infusion over 5 min, at least 15 min before skin incision.

- In the misoprostol group, 400 micrograms of misoprostol (2 tablets) were administered sublingually by the patients immediately before starting the skin incision.

- Following the baby’s delivery, all patients in the three groups received an intravenous bolus of 5 IU oxytocin and 20 IU oxytocin in 500 mL lactated Ringer’s solution (infused at a rate of 125 mL/h).

- All patients were observed for primary PPH for the first 24 h.

- They were also followed regarding the occurrence of misoprostol-related side effects (shivering, pyrexia>38°C, headache, nausea, and vomiting in the first 6 h) and the occurrence of tranexamic acid-related side effects (thromboembolic events within one week of delivery).

- CBC was repeated 12 h after delivery, and the estimated blood loss (EBL) after CS was calculated by this formula:

- $EBL = EBV \times \frac{\text{Pre} - \text{operative hematocrit} - \text{Post- operative hematocrit}}{\text{Pre} - \text{operative hematocrit}}$
- where EBV is the estimated blood volume of the patient in mL=weight in kg × 85

- The primary outcome was to compare the estimated blood loss (EBL) during and after cesarean delivery among the three groups, while the secondary outcomes were to evaluate the incidence of PPH and the possible side effects.

Sample size calculation

- The sample size was calculated with PASS 11 software. The sample size of 95 for each group achieves 90% power to detect a difference of 100.8 between the null hypothesis and the alternative hypothesis that their means are 499.9 and 600.7 with estimated group standard deviations of 206.4 and 215.7 and with a significance level (alpha) of 0.05 using a two-sided two-sample t-test.

- The sample size was increased by 20% to be 114 for each group to allow for dropouts.

Statistical methods

- Recorded data were analysed using the statistical package for the Social Sciences (SPSS) version 25.
- Quantitative variables were summarized in the form of mean and standard deviation, while categorical variables were summarized in the form of numbers and percentages.
- The numerical data were compared with a one-way analysis of variance (ANOVA) when comparing between means and with the Kruskall-Wallis test if the data were nonparametric.
- For comparing the categorical data, a Chi square (x2) test was performed. P values less than 0.05 were considered statistically significant.

Results

- In this clinical trial, 345 pregnant women met the inclusion criteria and assigned to three groups.

- Both tranexamic and misoprostol groups had similar results regarding the post-operative Hb and HCT, the reduction in Hb and HCT values, the blood loss in the suction apparatus and the EBL. There were no significant differences between both groups.

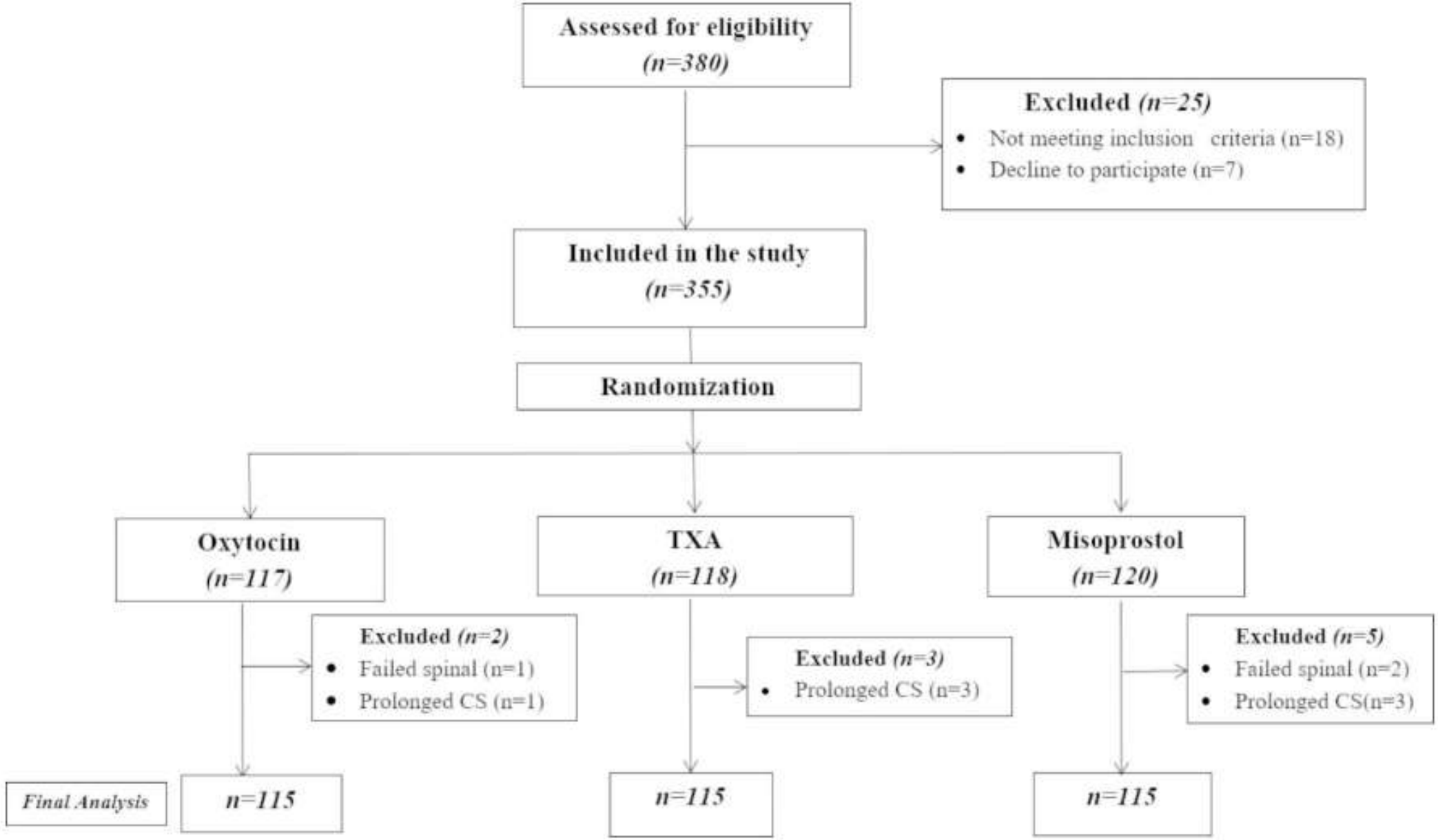

Fig. 1 Flow diagram of patients in the study

Table 1 Basic demographic and clinical characteristics of the participants

	Tranexamic Group (n = 115)	Misoprostol Group (n = 115)	Control Group (n = 115)	P-value
Maternal age (years)	29.59 ± 4.15	28.70 ± 4.51	29.90 ± 5.15	0.125
BMI (kg/m2)	30.56 ± 3.60	30.54 ± 4.30	30.19 ± 3.44	0.903
Parity	7 (6.09%)	8 (6.96%)	7 (6.09%)	0.480
- Primigravida	13 (11.30%)	9 (7.83%)	18 (15.65%)	
- Para 1	95 (82.61%)	98 (85.22%)	90 (78.26%)	
- Para 2 or more				
GA at delivery	38.46 ± 0.97	38.50 ± 0.96	38.38 ± 0.95	0.622
CS Indication	86 (74.8%)	86 (74.8%)	76 (66.1%)	0.667
- previous CS	3 (2.6%)	5 (4.3%)	8 (7.0%)	
- CPD	11 (9.6%)	9 (7.8%)	15 (10.4%)	
- Abnormal presentation	12 (10.4%)	11 (9.6%)	14 (12.2%)	
- Placenta Previa	3 (2.6%)	4 (3.5%)	2 (1.7%)	
- ICSI				
Pre-operative Hb (gm/dl)	11.17 ± 0.89	11.42 ± 1.05	11.21 ± 1.11	0.146
Pre-operative HCT (%)	34.20 ± 2.64	34.94 ± 3.42	34.70 ± 3.24	0.188
Estimated blood volume (ml)	7169 ± 546	7121 ± 719	7108 ± 556	0.726
CS Duration (minutes)	73.88 ± 14.95	77.19 ± 11.12	74.24 ± 15.26	0.142
Interval from skin incision to complete fetal and placental extraction (minutes)	15.15 ± 1.14	15.10 ± 0.89	14.95 ± 1.38	0.385

Table 2 Maternal outcomes in Caesarean section

	Tranexamic Group (n = 115)	Misoprostol Group (n = 115)	Control Group (n = 115)	P-value
Number of soaked towels	5 (2–10)	4 (2–9)	6 (2–10)	**< 0.001***
Blood loss in suction apparatus (ml)	247.4 ± 115.6	248.7 ± 93.5	395.2 ± 142.2	**< 0.001***
Post-operative Hb (gm/dl)	10.39 ± 0.87	10.58 ± 1.03	9.89 ± 1.07	**< 0.001***
Hb difference (gm/dl)	-0.78 ± 0.57	-0.83 ± 0.52	-1.32 ± 0.57	**< 0.001***
Post-operative HCT (%)	31.15 ± 2.62	31.88 ± 3.38	29.76 ± 3.07	**< 0.001***
HCT difference (%)	-3.05 ± 1.28	-3.06 ± 1.13	-4.94 ± 1.82	**< 0.001***
Estimated blood loss (ml)	641.6 ± 271.9	617.9 ± 207.4	1002.4 ± 340.7	**< 0.001***
Incidence of postpartum haemorrhage in 1st 24 h	2 (1.74%)	1 (0.87%)	3 (2.61%)	0.601
Side effects	1 (0.9%)	0 (0.0%)	0 (0.0%)	0.367

Table 3 Comparison between the three groups regarding

	Groups		Mean Difference (X-Y)	P-value	95% Confidence Interval	
					Lower	Upper
Post-operative Hb (gm/dl)	Control (X)	Tranexamic (Y)	-0.50	**<0.001***	-0.808	-0.192
		Misoprostol (Y)	-0.70	**<0.001***	-1.004	-0.388
	Tranexamic (X)	Control (Y)	0.50	**<0.001***	0.192	0.808
		Misoprostol (Y)	-0.20	0.294	-0.504	0.112
	Misoprostol (X)	Control (Y)	0.70	**<0.001***	0.388	1.004
		Tranexamic (Y)	0.20	0.294	-0.112	0.504
Hb difference (gm/dl)	Control (X)	Tranexamic (Y)	-0.54	**<0.001***	-0.708	-0.363
		Misoprostol (Y)	-0.49	**<0.001***	-0.659	-0.314
	Tranexamic (X)	Control (Y)	0.54	**<0.001***	0.363	0.708
		Misoprostol (Y)	0.05	0.779	-0.123	0.222
	Misoprostol (X)	Control (Y)	0.49	**<0.001***	0.314	0.659
		Tranexamic (Y)	-0.05	0.779	-0.222	0.123
Post-operative HCT (%)	Control (X)	Tranexamic (Y)	-1.39	**0.002**	-2.333	-0.446
		Misoprostol (Y)	-2.12	**<0.001***	-3.063	-1.175
	Tranexamic (X)	Control (Y)	1.39	**0.002**	0.446	2.333
		Misoprostol (Y)	-0.73	0.165	-1.673	0.214
	Misoprostol (X)	Control (Y)	2.12	**<0.001***	1.175	3.063
		Tranexamic (Y)	0.73	0.165	-0.214	1.673
HCT difference (%)	Control (X)	Tranexamic (Y)	-1.89	**<0.001***	-2.342	-1.446
		Misoprostol (Y)	-1.89	**<0.001***	-2.334	-1.438
	Tranexamic (X)	Control (Y)	1.89	**<0.001***	1.446	2.342
		Misoprostol (Y)	0.01	0.999	-0.440	0.456
	Misoprostol (X)	Control (Y)	1.89	**<0.001***	1.438	2.334
		Tranexamic (Y)	-0.01	0.999	-0.456	0.440
Estimated blood loss (ml)	Control (X)	Tranexamic (Y)	360.74	**<0.001***	274.219	447.260
		Misoprostol (Y)	384.43	**<0.001***	297.914	470.955
	Tranexamic (X)	Control (Y)	-360.74	**<0.001***	-447.260	-274.219
		Misoprostol (Y)	23.70	0.795	-62.825	110.216
	Misoprostol (X)	Control (Y)	-384.43	**<0.001***	-470.955	-297.914
		Tranexamic (Y)	-23.70	0.795	-110.216	62.825
Blood loss in suction apparatus (ml)	Control (X)	Tranexamic (Y)	147.83	**<0.001***	110.948	184.704
		Misoprostol (Y)	146.52	**<0.001***	109.644	183.399
	Tranexamic (X)	Control (Y)	-147.83	**<0.001***	-184.704	-110.948
		Misoprostol (Y)	-1.30	0.996	-38.182	35.573
	Misoprostol (X)	Control (Y)	-146.52	**<0.001***	-183.399	-109.644
		Tranexamic (Y)	1.30	0.996	-35.573	38.182

[a] P-value is significant (ANOVA test with Tukey Post Hoc test)

Discussion

- In this study, the combined use of sublingual misoprostol and IV oxytocin was equally effective as the combined use of IV tranexamic acid and oxytocin in decreasing blood loss in high-risk women undergoing CS. Meanwhile, compared to using oxytocin alone, both protocols were superior in reducing the amount of blood loss.

- Hemapirya L et al. (2020) reached similar results, who were randomized equally randomized into two groups; the study group in which tranexamic acid was given before skin incision, and a control group which was given the standard oxytocin intravenously following the delivery of the baby.

- The study group had less blood loss and higher post-operative hemoglobin when compared to the control group.

- In a meta-analysis by Simonazzi et al. (2016) that included 2365 women from nine trials, the pre-operative use of tranexamic acid was associated with lower blood loss, less hemoglobin drop and lower incidence of PPH; when compared to the control who had oxytocin alone.

- Regarding the role of adding sublingual misoprostol to oxytocin in preventing PPH, previous studies revealed similar results to our finding.

- Chaudhuri and Majumdar (2015) studied the effect of sublingual misoprostol in a dose of 400 mcg versus placebo in 198 women undergoing emergency CS and at high risk for blood loss.

- In their study, misoprostol was given following delivery of the baby, unlike in our study, in which misoprostol was given before skin incision.

- They also used 20 U of oxytocin IV following delivery of the baby in both groups, whereas we used 10 U of oxytocin.

- The misoprostol group showed a significantly lower mean intraoperative blood loss compared to the placebo group; however, the post-operative blood loss was slightly lower in the misoprostol group.

- Side effects such as shivering and pyrexia were reported more in the misoprostol group.

- In a former study, Fekih et al. compared the role of sublingual misoprostol administration (in a dose of 200 mcg) at cord clamping together with oxytocin at a dose of 20 U (10 U bolus dose and 10 U infusion in 500 ml lactated Ringer), with that of giving oxytocin alone at the same dose.

- The combined misoprostol and oxytocin group showed less blood loss and less hemoglobin drop than the oxytocin-only group.

- The strength of our study is comparing the effectiveness and safety of sublingual misoprostol to that of IV tranexamic acid, as well as to that of oxytocin alone in preventing PPH in high-risk pregnant women undergoing CS.

Limitation of the study

- However, the main limitation is that our study was open-label, and our population had various risk factors. Also, we did not study the effect of different doses of misoprostol.

Conclusion

- In clinical practice, both IV tranexamic acid and sublingual misoprostol, when used along with oxytocin, are equally capable of reducing blood loss.

- However, the results were significantly better than using oxytocin alone in high-risk patients.

- Further studies in the future are needed, especially in low-risk patients, due to the discrepancy in the results of the previous studies.

- **Acknowledgements**

None

- **Authors' contributions**

O.H. and M.E. designed and supervised the study. M.D., M.A., and M.S. conducted the study. M.A.R. analyzed the data. All authors wrote and approved the manuscript.

- **Funding**

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Declarations

- **Ethical approval**

The study protocol was approved by Kasr El-Ainy Ethical Committee. All methods were carried out following the relevant guidelines and regulations. Informed consent was obtained from all participants.

- **Consent for publication**

Not Applicable

- **Informed consent**

All participants gave their consent after being informed of the study's objective and design, and they were given the option to leave the study at any time.

- **Competing interests**

The authors declare no competing interests.

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Critical appraisal

Title

Intravenous tranexamic acid vs. sublingual misoprostol in high-risk women for postpartum haemorrhage following cesarean delivery; a randomised clinical trial

Suggested Title

Comparison of efficacy and safety of Intravenous tranexamic acid and Oxytocin vs sublingual misoprostol and Oxytocin in high-risk women for postpartum haemorrhage following cesarean delivery; An Open label randomised clinical trial

Critical appraisal based on CONSORT checklist

Sr no.	Title	Justifiable	Not Justifiable	Comments
1.	Title & Abstract	✓		• Identification as a randomized trial in the title • Structured summary of trial design, methods, results, and conclusions are given
	Introduction			
2a	Background	✓		• Scientific background and explanation of rationale
2b	Objectives		✓	• Specific objectives or hypotheses are not given

Methods

Trial design				
Sr no.	**Title**	**Justifiable**	**Not Justifiable**	**Comments**
3a	Description of trial design (such as parallel, factorial) including allocation ratio		✓	• Trial design is not mentioned • Allocation ratio is not mentioned
3b	Important changes to methods after trial commencement (such as eligibility criteria)	✓		• No changes in methods after trial commencement

Participants

Sr no.	Title	Justifiable	Not Justifiable	Comments
4a	Eligibility criteria for participants		✓	• Inclusion and exclusion criteria are mentioned, but failed spinal exclusion criteria is not mentioned
4b	Settings & locations where the data were collected	✓		• Single centred study at Kasr Al-Ainy Hospital, Egypt
• **Interventions**				
5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	✓		• 1 gm (10 ml) of tranexamic acid was diluted in 20 ml of Glucose 5% given to an intravenous infusion over 5 min, at least 15 min before skin incision • 400 micrograms of misoprostol (2 tablets) sublingually before starting the skin incision

Outcomes & Sample size

Sr no.	Title	Justifiable	Not Justifiable	Comments
6	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	✓		The primary outcome was to compare the estimated blood loss (EBL) during and after cesarean delivery among the three groups, secondary outcomes were to evaluate the incidence of PPH and the possible side effects.
7a	How sample size was determined	✓		• calculated with PASS 11 software.Formula used with 5% significance level and 90% of power
7b	When applicable, explanation of any interim analyses and stopping guidelines			NA

Randomisation

Sr no.	Title	Justifiable	Not Justifiable	Comments
8a	Method used to generate the random allocation sequence	✓		• computer-generated random numbers.
8b	Type of randomization		✓	• Not mentioned
9	Mechanism used to implement the random allocation sequence	✓		• computer-generated
10	Implementation		✓	• Not mentioned

Sr no.	Title	Justifiable	Not Justifiable	Comments
11	Blinding		✓	• Open label study
12	Statistical methods	✓		• The numerical data were compared with a one-way analysis of variance (ANOVA) when comparing between means and with the Kruskall-Wallis test if the data were non-parametric. • For comparing the categorical data, a Chi-square (x2) test was performed.

Results

Sr no.	Title	Justifiable	Not Justifiable	Comments
13	Participants flow	✓		• 345 pregnant women were assigned • For each group, exclusions after randomization, together with reasons are mentioned
14	Recruitment	✓		• Dates defining the periods of recruitment is mentioned from January 2020 to December 2020
15	Baseline data	✓		• Baseline data are mentioned

Sr no.	Title	Justifiable	Not Justifiable	Comments
16	Outcomes & estimation	✓		Estimated effect size and its precision are mentioned (such as 95% confidence interval is mentioned)

Discussion

Sr no.	Title	Justifiable	Not Justifiable	Comments
17	Limitations	✓		• Trial limitations are mentioned
18	Generalisability		✓	• Not mentioned
19	Interpretation		✓	• Results, balancing benefits,harms and other relevant evidence is mentioned ,but treatment of PPH are not mentioned.

Other Information

Sr no.	Title	Justifiable	Not Justifiable	Comments
20	Registration	✓		• Registration number and name of trial registry is mentioned
21	Protocol			NA
22	Funding		✓	• No specific grant from any funding agency, but funding provided by The Egyptian Knowledge Bank (EKB).

Thank you