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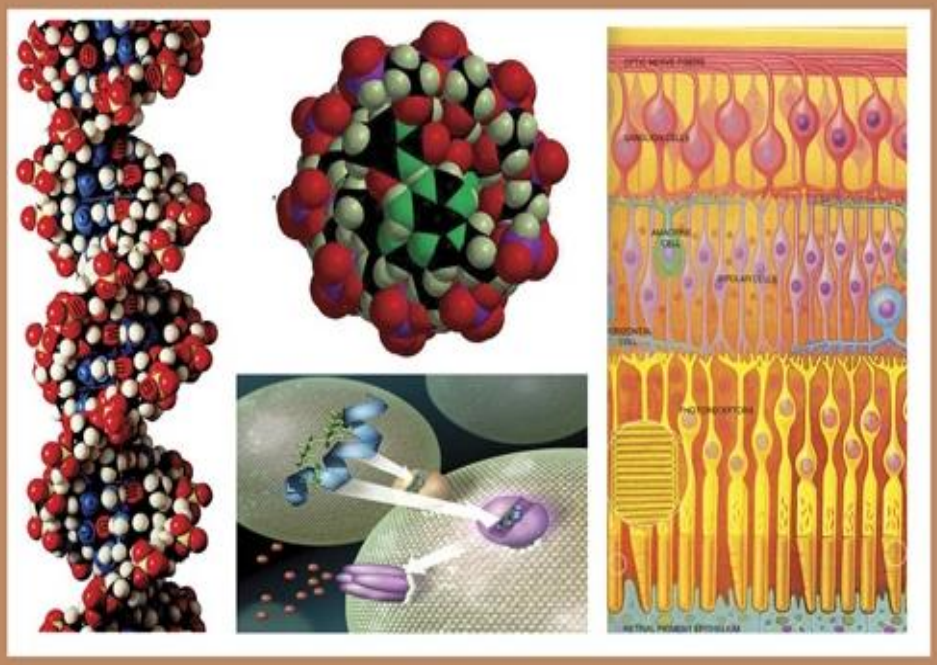

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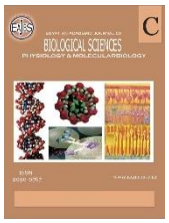

Comparative Study of Oxytocin Versus Tranexamic Acid and Ethamsylate for Reducing Blood Loss in Patient Undergoing Lower Segment Elective Cesarean Section at High Risk for Post-Partum Haemorrhage

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ABSTRACT

Background: Worldwide, twenty-one per cent of deliveries are by elective cesarean Sections (C/S) as a lifesaving procedure to diminish maternal and neonatal mortality. Blood loss during C/S is more than that during vaginal delivery. Therefore, reducing blood loss during the C/S is essential and challenging for Anaesthesiologists. This study aimed to assess the efficacy of intravenous oxytocin and tranexamic acid + ethamsylate (TXA+Eth) in reducing blood loss in the elective lower segment (L/S) C/S in pregnant at high risk for postpartum haemorrhage (PPH). **Methods:** A single-centre, prospective, randomised, and double-blind study was started after obtaining institutional ethical approval among gravid undergoing elective L/S C/S at full-term pregnancy at high risk for PPH at the SAMSRI between September 2021 and March 2022. Study participants received an infusion of either oxytocin 10 International Unit (IU) or TXA 1 g + Eth 250 mg before the skin incision for C/S. The primary outcome was the blood loss calculation, along haemoglobin and haematocrit before and after the surgery. The secondary outcome was the percentage of participants who progressed into PPH and required blood transfusion. **Results:** Analyses included 132 women in each group, and results showed that TXA + Eth significantly reduced bleeding during and after cesarean delivery in pregnant at high risk for PPH. In oxytocin and TXA + Eth groups, postoperative blood loss was (613.7 ±123.7 and 406.2±116.5) ml, respectively, $p<0.001$. The duration of surgery (DOS) in oxytocin and TXA + Eth groups were (48.5±9.3) and (44.3±9.8) minutes, respectively ($p= 0.287$). The blood transfusion requirement in the oxytocin and TXA + Eth groups were 10.69% and 0.75%, respectively ($p= 0.023$). The PPH in the oxytocin and TXA + Eth groups were 2.30% and 0%, respectively ($p<0.017$). Pre and postoperative haemoglobin and haematocrit values at 12 hours after C/S in the oxytocin (10.78 and 8.29) and (32.23+25.10) and TXA + Eth groups were (11.07 and 10.02) and (33.20 and 30.73), respectively ($p < 0.001$). **Conclusion:** The use of TXA and Eth is safe and more effective than oxytocin in minimizing blood loss during C/S, the demand for blood transfusion, with the stability of haematologic profile during cesarean delivery.

INTRODUCTION

Elective cesarean delivery is a planned, lifesaving procedure through incisions of the abdomen lower uterine segment of the mother at the fetus's viability when the vaginal labour would situate to maternal and fetal morbidity and mortality (Gibbons L, *et al.,* 2012). Cesarean Sections (C/S) be performed only if medically obligatory in 10-15% population, as stated by the World Health Organization (WHO 2015). The worldwide rate of C/S is 21% and is expected to increase to 29% by 2030 (WHO 2021). The rate of C/S in some states of India, such as Kerala, Andhra Pradesh, and Jammu and Kashmir, is above 40% (Roy N., *et al.,* 2021).

Worldwide, one-fourth of all maternal deaths are caused by postpartum haemorrhage (PPH), and PPH is diagnosed if blood loss is ≥700 ml (Kramer M.S., *et al.,* 2013). Its most common risk factors include multiple pregnancies, macrosomia, polyhydramnios, and previous PPH. PPH could be avoided most of the time through the prophylactic use of uterotonics agents (Bateman BT, *et al.,* 2010). Therefore, drugs such as ergometrine, oxytocin, Misoprostol, Carbetocin, and carboprost were tested previously to reduce perioperative blood loss during C/S (Prevention and Management of Postpartum Haemorrhage 2017).The British journal of Obstetricians and Gynecologists (BJOG) emphasises slow intravenous use of oxytocin 5 International Unit (IU) after fetal labour to urge contractions of the uterus, and hence, decrease intra-operative blood loss and thereby PPH (Prevention and Management of Postpartum Haemorrhage 2017). Efforts are made to prevent and control perioperative haemorrhages in high-risk PPH candidates. Prophylactic antifibrinolytic and haemostatic therapy is another approach to reducing haemorrhage using prohaemostatic drugs such as TXA and Eth (Singh S., *et al.,* 2022). TXA is a synthetically derived amino-acid lysine that exerts its antifibrinolytic action through the reversible block of the lysine binding sites on the proenzyme plasminogen molecule (Singh S., *et al.,* 2022). TXA has been routinely used for preventing and treating bleeding with promising results (Prevention and Management of Postpartum Haemorrhage 2017and Novikova N., *et al.,*2015).

Eth is a commonly available synthetic haemostatic drug that exerts its effect by improving platelet adhesiveness and restoring capillary endothelial resistance. In addition, the drug exerts anti-hyaluronidase action and improves capillary wall stability. Thus, it reduces capillary bleeding when platelets are inadequate in the blood. It also inhibits Prostacyclin I_2 synthesis and normalises abnormal platelet function (Elbourne D., 2001 and Suryakumari B. and Parveen S. *et al.,* 2017).

Some studies conducted in the past have shown that the use of TXA reduces bleeding and PPH (Prevention and Management of Postpartum Haemorrhage 2017 and Novikova N., *et al.,*2015). and in contrast, few studies have reported no significant reduction in active bleeding with the addition of TXA to misoprostol treatment (Diop A., *et al.,* 2020). Dixon and colleagues demonstrated in 2020 that there are no differences between activated partial thromboplastin time (aPTT), prothrombin time (PT), thrombin antithrombin, fibrinogen, international ratio (INR), plasminogen activator inhibitor, and tissue plasminogen activator (tPA) in placebo and TXA groups at 6 hours after administration (Dixon AL, *et al.,* 2020). Wilde and colleagues reported no difference in blood loss between patients treated with one and two doses of TXA (Wilde J.M., *et al.,*2022). World Maternal Antifibrinolytic (WOMAN) Trial Collaborators reported no benefit from TXA administered more than 3 hours postpartum (WOMAN Trial Collaborators 2017). There is a controversy in the literature about the dose, timing of administration, and effectiveness of TXA in pregnant women at high risk of PPH [Suryakumari B. and Parveen S.. *et al.,* 2017 ;Dixon AL, *et al.,*

2020 and Singh LC, *et al.*, 2022). There is a paucity of clinical trials that investigated the role of Eth in either prophylaxis or treatment of PPH. This study aimed to compare the efficacy and safety of intravenous oxytocin and TXA + Eth in reducing blood loss during the intra-operative and postoperative period after elective L/S C/S in patients at high risk for PPH.

MATERIALS AND METHODS

This was a single-centre, prospective, randomised, and a double-blind study conducted at SAMSRI, Lucknow, India, between September 2021 and March 2022 after approval from the Institutional Ethical Clearance Committee on Human Research (Number: OBGH/1837/R/2021-22) SAMSRI, Lucknow, India. Sixty-four women in the age group of 20-40 years, with no medical disorders, at 38 - 40 weeks of gestation are at high risk for PPH (with one or more risk factors for PPH such as macrosomic baby [weight > 4.5 kg]), multiple pregnancies, polyhydramnios [AFI > 25 cm], obesity [BMI > 30], previous history of PPH) and planned for elective L/S C/S were eligible for surgery. Exclusion criteria included anaemia, acute kidney or liver diseases, history of convulsions, deep venous thrombosis (DVT), the bleeding tendency (disseminated intravascular coagulopathy-DIC), prolonged bleeding time/ prothrombin time/ thrombin time, disturbances of colour vision, abnormal placentation (such as placenta previa, abruptio placenta, or morbidly adherent placenta), allergy to TXA or Eth.

Data from the pilot study revealed that the risk of postpartum blood loss ≥500 ml was 11.82% in women who received TXA 1gm + Eth 250 mg in contrast to 28.94% in women who received Oxytocin 10 IU alone. Calculation according to these values produced a minimal sample size of 120 cases per group. We derived a mean difference of 9% with an SD of 17% from our pilot data and calculated that woman per group would be needed with a two-sided α error of 0.05 and power of 0.8. A 10% of the dropout was also added to the sample size. The required sample size (n) = [(estimated 120 and dropout 12)] =132 cases per group.

After ethical approval, study participants were involved in a discussion on the nature of the study, and informed written consent was obtained on the day of their scheduled L/S C/S. To sample 64 participants who met the eligibility criteria were identified each weekday from the registry of the theatre manager's surgical caseloads, a balloting system was used with a total of 30 sheets of papers equally assigned 'In' and 'Out' for them to pick one at the point of recruitment. Those who selected 'In' were enrolled till the sample size of 64 was reached to give an equal chance to the study population. Randomisation of participants was performed using a computer-generated randomisation programme. To double-blind, neither the investigator nor the patient knew about the study drugs. For both groups, a 50 ml syringe was used to dilute study drugs in 0.9% NaCl to make it 50 ml and infused at a rate of 50ml/hour before taking the skin incision with an infusion pump.

The day before surgery, all participants underwent a pre-anaesthetic evaluation. A detailed examination of the cardiovascular, respiratory, and central nervous systems was performed. For all gravid, weight, nutritional status, and airway assessment by the Mallampatti scoring system were recorded. In addition, preoperative Obstetric ultrasonography to check fetal heart rate and routine investigations such as platelet count, haemoglobin, haematocrit, and blood group/Rh typing were rechecked. The spinal anaesthesia procedure was explained to the participants on the day of surgery, and written informed consent was obtained for anaesthesia and the surgery.

Intravenous access was secured, and Ringer's lactate solution infusion started. Patients were then shifted to the operating room, after which routine non-invasive monitoring was applied and vital signs monitored. After preloading the gravid with

Ringer lactate 15 ml/kg, in a lateral position, lumbar puncture was performed at L3-4 level with Quincke type pencil-point 25 G X 90mm disposable spinal needle. Injection bupivacaine 0.5% (Anawin heavy from Neon, India) 1.75 ml solution was injected intrathecally over 30 seconds and then turned to supine position. Then, the surgeon started painting and draping the operating field and took the skin incision after confirming an adequate level of sensory loss. As per the group allocation injection, TXA 1gm (Tranexanaman from Naman Global Impex Pvt. Ltd, India) + Eth 250 mg (Ethamo from Zydus India) or oxytocin, 10 IU (Evatocin from Neon, India) infusion in 50 ml 0.9% NaCl, at a rate of 50ml/hour was started before the start of the skin incision with an infusion pump.

Mean arterial pressure (MAP), heart rate (HR), and oxygen saturation (SpO_2) were monitored regularly throughout the surgery. Any fall in the HR below 60 beats per minute and MAP below 65mmHg were considered bradycardia and hypotension, respectively, and treated with incremental doses of Injection atropine 0.3 mg IV and injection of Ephedrine 10 mg, respectively. If any patient developed any complications was treated appropriately and excluded from the study.

Two variants calculated blood loss. The primary outcome was the blood loss calculation by calculating the difference between the weight of dry and wet gauzes and drapes soaked in blood and suctioned blood, along with the difference between haemoglobin and haematocrit before and after the surgery. The secondary outcome was the percentage of participants who progressed into PPH and required blood transfusion. Participants were given a brief orientation regarding signs and symptoms of a thromboembolic event and instructed to contact the investigating team member in case of need. All participants were examined for thromboembolic signs on follow-up at the 1 and 4 weeks.

Descriptive statistics for measured variables are expressed as a range, mean and standard deviation (for metric data); range, median and inter-quartile range (for discrete data); and number and proportions (for categorical data). Data of both groups were compared using a t-test (for quantitative parametric measures), Mann-Whitney's U-test (for quantitative nonparametric measures), and Fischer's Exact tests (for categorical measures). $P < 0.05$ was considered significant. Statistical analysis was performed using Statistical Package for Social Sciences SPSS -23.0; IBM, Armonk, NY, the USA for Windows was used.

RESULTS

Two hundred and sixty-four women who received either oxytocin 10 IU or TXA 1gm + Eth 250 mg were recruited during the study period. However, data from 263 (99.63%) women were analysed. one woman (0.37%) was excluded from the study analysis due to sample attrition in the oxytocin group. The age, BMI, and gestational age in oxytocin and TXA + Eth groups were (29.0±4.4 and 28.5±4.3 years), (28.5±5.2 and 26.1±5.6 kg/m^2) and (38.92±0.40 and 38.87±0.40weeks), respectively. There was no significant difference in demographic between the oxytocin and TXA + Eth groups ($p>0.05$) (Table-1).

Table 1. Demographic comparison between the two study groups.

Variables	Oxytocin Group Mean±SD (Range) n=131	TXA + Eth Group Mean±SD (Range) n=132	p-value
Age (yrs)	29.0±4.4 (20-35)	28.5±4.3 (22-34)	0.285
BMI (kg/m^2)	28.5±5.2 (22.4–29.7)	26.1±5.6 (19.1–29.9)	0.209
Gestational age (wks)	38.92±0.40 (38.0-41.0)	38.87±0.40 (38.0-41.0)	0.621
Parity Nulli Multi	 48.0% 52.0%	 56.0% 44.0%	0.25

Kg = Kilogram, m= Metres, n=Number, SD= standard deviation, Yrs = Years, weeks=wks, p-value is significant <0.05.

There was a significant difference between the oxytocin and TXA + Eth groups regarding postoperative blood loss (613.7 ±123.7 and 406.2±116.5) ml, respectively, p<0.001. The duration of surgery in oxytocin and TXA + Eth groups were (48.5±9.3) and (44.3±9.8) minutes, respectively. The duration of surgery was less in TXA + Eth group but statistically insignificant between the two groups (p= 0.287) (Table-2).

Table 2. Comparison of intra-operative variables among the two study groups.

Variables	Oxytocin Group Mean±SD (Range) n=131	TXA + Eth Group Mean±SD (Range) n=132	P-value	Effect size Mean±SE 95% CI
Blood loss (mL)	613.7 ±123.7 (413.0–889.0)	406.2±116.5 (241-694.0)	<0.001*	-206.8±15.7 (-242.4 173.1)
DOS (minutes)	48.5±9.3 (26.0–61.0)	44.3±9.8 (29.0–59.0)	0.287	-1.5±1.4 (-3.3-1.4)

DOS= Duration of surgery, ml= Millilitre, n=Number, SE=standard error

The blood transfusion requirement in the oxytocin and TXA + Eth groups were 10.69% and 0.75%, respectively. The blood transfusion during surgery was statistically significant between the two groups (p= 0.023). The PPH in the oxytocin and TXA + Eth groups were 2.30% and 0%, respectively, and the PPH case in the oxytocin group were significantly more (p<0.017) (Table-3).

Table 3. Comparison of postoperative blood transfusion among the two study groups.

Variables	Oxytocin Group (n=131) N (%)	TXA+Eth Group(n=132) N (%)	Fisher exact test	P-value
Blood transfusion			1.96	0.023*
Yes	14 (10.69%)	1 (0.75%)		
No	117 (89.31%)	131 (99.25%)		
PPH			2.18	0.017*
Yes	3 (2.30%)	0 (0%)		
No	128 (97.70%)	132 (100%)		

PPH= Postpartum haemorrhage

In our study, pre-and postoperative haemoglobin values at 2 hours after C/S in the oxytocin and TXA + Eth groups were (10.78 and 11.07) and (9.33 and 10.81), respectively. Postoperative haemoglobin was significantly higher in the TXA + Eth group 2 hours after C/S than in the oxytocin group (p < 0.001). Also, postoperative haematocrit was significantly higher in the TXA + Eth group than in the oxytocin group at 2 hours after C/S (p < 0.001). These findings of haemoglobin and haematocrit support each other (Table-4; Figs.-1 & 2

Table 4. Comparison of perioperative variables among the two study groups 2 hours after C/S.

Variables	Oxytocin Group Mean±SE (Range) 95% Confidence Interval n=131	TXA+Eth Group Mean±SE (Range) 95% Confidence Interval n=132	Repeated measures ANOVA test	P-value
Preoperation Hb gm/dl	10.78±1.34 (10.51-11.04)	11.07±0.14 (10.81-11.34)	70.67	<0.001*
Postoperation Hb gm/dl	9.33±1.31 (9.07-9.59)	10.81±0.13 (10.55-11.07)		
Preoperation Hct%	32.23±0.39 (31.45-32.99)	33.20±0.39 (32.43-33.98)	57.96	<0.001*
Postoperation Hct%	28.20±0.40 (27.32-28.89)	32.42±0.40 (31.64-33.21)		

gm/dl = *grams* per deciliter, Hb= haemoglobin, Hct=haematocrit, SE=standard error**.**

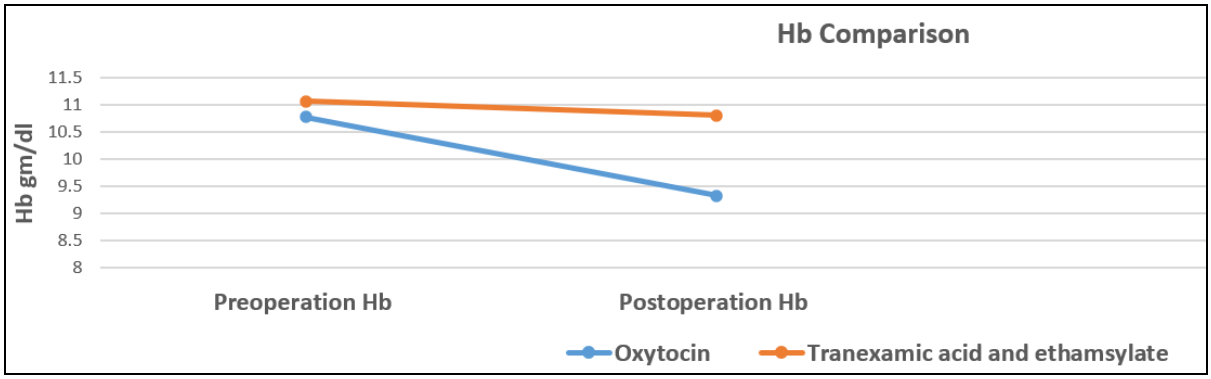

Fig. 1. Comparison of haemoglobin levels between the two groups**.**

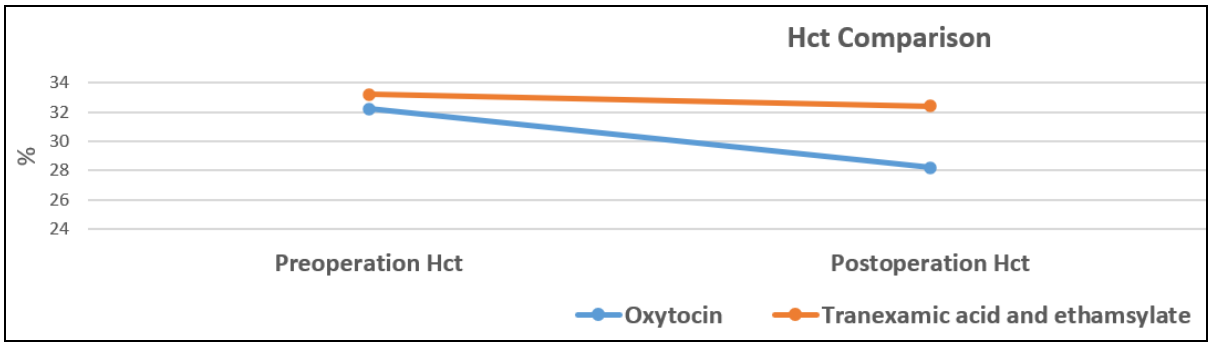

Fig. 2. Comparison of haematocrit levels between the two groups.

Pre-and postoperative haemoglobin and haematocrit values at 12 hours after C/S in the oxytocin (10.78 and 8.29) and (32.23+25.10) and TXA + Eth groups were (11.07 and 10.02) and (33.20 and 30.73), respectively. However, postoperative haemoglobin was significantly higher in the TXA + Eth group 12 hours after C/S than in the oxytocin group ($p < 0.001$). Also, postoperative haematocrit was significantly higher in the TXA + Eth group than in the oxytocin group 12 hours after C/S ($p < 0.001$). These findings of haemoglobin and haematocrit support each other (Table-5).

Table 5. Comparison of perioperative variables among the two study groups 24 hours after C/S:

Variables	Oxytocin Group Mean±SE (Range) 95% Confidence Interval n=131	TXA+Eth Group Mean±SE (Range) 95% Confidence Interval n=132	Repeated measures ANOVA test	P-value
Preoperation Hb gm/dl	10.78±1.34 (10.51-11.04)	11.07±0.14 (10.81-11.34)	69.28	<0.001*
Postoperation Hb gm/dl	8.29±1.18 (7.01-9.82)	10.02±0.10 (9.27-10.75)		
Preoperation Hct%	32.23±0.39 (31.45-32.99)	33.20±0.39 (32.43-33.98)	55.82	<0.001*
Postoperation Hct%	25.10±0.30 (26.20-28.18)	30.73±0.36 (31.24-33.05)		

gm/dl = *grams* per deciliter, Hb= haemoglobin, Hct=haematocrit, SE=standard error

DISCUSSION

Abdominal delivery, known as a caesarean section, is a lifesaving procedure for the extraction of the fetus through the surgical incision of the anterior abdominal wall and then the incision of the lower segment of the uterus. C/S delivers one million gravid women yearly worldwide. The rate of C/S raised from 5.6% in 1970 to 32% in 2019 and is expected to increase to 39% by 2030 (WHO 2021). In Indian states, Jammu & Kashmir, Kerala, and Andhra Pradesh C/S rate is more than 40% (Roy N., *et al.*, 2021).

Obstetric haemorrhage contributes to about 25% of maternal deaths worldwide, and PPH is a well-known complication that increases the re-exploration rate, blood

transfusion requirement, length of hospitalisation (LOH), and cost. Therefore, every effort is made to prevent and control bleeding after surgery. Prophylactic antifibrinolytic and haemostatic therapy is one approach to reducing postoperative bleeding. In 2017, WHO recommended using antifibrinolytic for the treatment of PPH in case oxytocin and other ecbolics fail to stop the haemorrhage during vaginal delivery, regardless of the cause (World Health Organization 2017).

The aprotinin was the only extensively evaluated natural antifibrinolytic agent. However, the blood conservation using antifibrinolytics in a randomised trial **(**BART) showed an increased risk of allergic reaction and thrombosis leading to death with aprotinin, limiting its use (Faraoni D., 2020). Therefore, the commonly available antifibrinolytics are tranexamic acid (TXA) and epsilon aminocaproic acid (EACA), which are synthetic, cheaper, and readily available. Although some studies do not show any difference between TXA and EACA (Elbourne D., *et al.* 2001), while others have shown that TXA is a more potent blood-sparing agent than EACA (Singh LC, *et al.,* 2022 and Leff J., *et al.*, 2019), these findings encouraged us to consider TXA over EACA for pregnant at high risk for PPH.

Literature highlights the possible adverse effects of antifibrinolytics, especially with the TXA, such as seizures (Keyl C., *et al.*, 2011 and Martin K., *et al.*, 2008) and renal dysfunction (Singh S, *et al.*, 2022). For example, Martin et al. reported that 4.6% of patients had seizures who received 2 g TXA at the beginning of surgery and then a continuous infusion of 0.5 g/h till the end of surgery (Martin K., *et al.*, 2008). It is worth noting that these participants were exposed to a very high dose of TXA. In contrast, we used 1gm of TXA as a continuous infusion. Seizure and renal dysfunction were not reported in our study. However, the manufacturer's package insert indicates that TXA may cause focal and generalised seizures.

Clinical randomisation of an antifibrinolytic in a significant haemorrhage-2 (CRASH-2) study showed that the use of TXA three hours after injury was associated with an increase in mortality, which suggests administering TXA at the earliest possible (CRASH-2 Collaborators 2011). Therefore, in agreement with the CRASH-2 study, TXA was started before the skin incision in this study.

Torky and colleagues 2021, compared the effectiveness of TXA+ Eth with placebo in reducing blood loss during elective C/S and concluded that both the drugs effectively reduce blood loss than placebo (Torky H., *et al.*, 2020). Overall, the findings of our study match the findings of the study mentioned above. In our study, postoperative blood loss in oxytocin and TXA + Eth groups was 613.7 and 406.2 ml, respectively, significantly less in the TXA+ Eth group ($p<0.001$) than oxytocin group. In addition, the haemoglobin and haematocrit were also significantly higher in the TXA group, which is consistent with the recommendations of The British Journal of Obstetricians & Gynecologists that TXA effectively reduces blood loss during vaginal delivery (Prevention and Management of Postpartum Haemorrhage 2017).

In contrast, Diop and colleagues 2020 reported that controlling active bleeding in PPH with TXA + misoprostol and placebo +misoprostol was (56.9% TXA) and (60.2% placebo), respectively ($p = 0.59$) (Diop A, *et al.,* 2020). TXA showed an insignificant result compared to placebo in their study, which may be due to the different routes of drug administration and study design. Diop and colleagues administered TXA orally, which may not confer the same effect as intravenous administration of TXA due to slow oral absorption and less bioavailability.

The present study showed that the duration of surgery (DOS) was shorter in the TXA + Eth group ranging from 29.0–59.0 (44.3) minutes, than in the oxytocin group ranging from 26.0–61.0 (48.5) minutes. Furthermore, the current result concurs with

the study of Suryakumari and Parveen (Suryakumari B and Parveen S. *et al.*, 2017) as they revealed that DOS was reduced in TXA + Eth groups due to less bleeding and wastage of less time to secure bleeder. However, in their study DOS was statistically significant, $p<0.05$, in contrast to statistically insignificant ($p=0.287$) in our study.

Our study supports the WOMAN Trial (WOMAN Trial Collaborators 2017), strengthening the place of TXA in PPH. WOMAN trial compared 1 gm TXA or placebo and concluded TXA decreased death due to bleeding [155 (1.5%) vs 191 (1.9%)] and laparotomy for bleeding was also reduced [82 (0.8%) vs 127 (1.3%), RR 0.64; 95% CI 0.49 - 0.85; $p = 0.002$] after vaginal delivery and C/S with no adverse effects. There was a significant difference between the oxytocin and TXA + Eth groups in postoperative blood loss (613.7 ±123.7 and 406.2±116.5) ml, respectively, $p<0.001$. Supported by pre and postoperative values of haemoglobin and haematocrit at 12 hours after C/S were (10.78 and 8.29) and (32.23 and 25.10) in the oxytocin group (11.07 and 10.02) and (33.20 and 30.73) in TXA + Eth group, respectively ($p < 0.001$).

There is a paucity of clinical trials investigating the role of Eth in either prophylaxis or treatment of postpartum haemorrhage. Our study was the first to use TXA and Eth to reduce blood loss in the elective lower segment C/S in pregnant women at high risk for postpartum haemorrhage, giving it a pilot nature.

Conclusion: The current results demonstrated that tranexamic acid and ethamsylate could be safely used to reduce bleeding during C/S in pregnant women at high risk for postpartum haemorrhage. TXA + Eth appears to be a safe and effective option in treating obstetric hemorrhage. Further research with large numbers of patients with different dosage and administration routes is preferable to compare each route's efficacy.

Data Availability: All the data are available within the manuscript. In addition, the datasets used and analysed during the current study are available from the corresponding author based on reasonable request.

Ethical Approval: Ethical clearance and approval were obtained through the Department of Anaesthesiology and Intensive Care at the SAMSRI, Lucknow, after approval from the Institutional Ethical Clearance Committee on Human Research (Number: OBGH/1837/R/2021-22) SAMSRI, Lucknow, India.

Consent: The study was explained to the patients, and written informed consent was obtained from them. Patients were informed that the care would not be compromised in any way, and their confidentiality was assured. Name and other identifying information were not used in the study.

Disclosure: The authors declare that this paper is their original work and has never been published. However, all directly quoted material has been appropriately referenced.

Funding Statement: This study did not receive any funding in any form.

Conflicts of Interest: The authors declare that they have no conflicts of interest.

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