

A COMPARATIVE STUDY OF TRANEXAMIC ACID VERSUS ETHAMSYLATE USED PROPHYLACTICALLY IN LOWER SEGMENT CAESAREAN SECTION- A PROSPECTIVE RANDOMISED DOUBLE-BLINDED STUDY

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ABSTRACT

BACKGROUND

Recently, caesarean section rates are increased in developing countries like India. Postpartum haemorrhage is more after caesarean section. Most of the maternal mortality is attributed to postpartum haemorrhage. This study was undertaken to find out the drug effective in reducing blood loss in lower segment caesarean section.

The aim of the study is to compare the efficacy of ethamsylate versus tranexamic acid in reducing blood loss during and after caesarean section.

MATERIALS AND METHODS

All women undergoing LSCS were divided in 3 groups, viz. 2 study groups and control group. All were requested for preop and postop Hb%, PCV and TRBC. Tranexamic acid and ethamsylate, 1 g diluted in 10 mL NS were given intravenously for both the study groups and control group with NS, 20 minutes prior to skin incision and blood loss was measured from placental delivery up to 2 hours in all the groups was calculated by weighing pre-weighted pads soaked in blood.

RESULTS

Statistical analysis was done quantitatively by Student's t-test. Postoperative blood loss was similar and lower in both the study groups compared to the control group. Hb% change in postop period is significant in control group.

CONCLUSION

Ethamsylate is safe and effective alternative to tranexamic acid in preventing postpartum haemorrhage after caesarean section.

KEYWORDS

Tranexamic Acid, Ethamsylate, Postpartum Haemorrhage, Caesarean Section.

HOW TO CITE THIS ARTICLE: Suryakumari B, Parveen S. A comparative study of tranexamic acid versus ethamsylate used prophylactically in lower segment caesarean section- A prospective randomised double-blinded study. J. Evid. Based Med. Healthc. 2017; 4 (75), 4435-4438. DOI: 10.18410/jebmh/2017/883

BACKGROUND

Rate of postpartum haemorrhage is more after C-section 4% vs. 0.6%¹ than vaginal delivery, among these 6%.^{2,3} requires blood transfusion and 11%⁴ suffers from severe postpartum anaemia. Recently, caesarean section rates have increased to as high as 25-30%⁵ in many developing countries of the world like India. Maternal mortality ratio is 174⁶ in India and mostly attributed to PPH, sepsis and eclampsia. Therefore, selection of effective prevention and treatment of PPH after CS should be important. Haemorrhage constitute 35% of maternal deaths globally.⁷ Such preventive agents are tranexamic acid and ethamsylate.

*Financial or Other, Competing Interest: None.
Submission 10-08-2017, Peer Review 15-08-2017,
Acceptance 30-08-2017, Published 16-09-2017.*

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DOI: 10.18410/jebmh/2017/883*



Tranexamic Acid- Mechanism of Action- Tranexamic acid (trans-4-aminomethylcyclohexane-i-carboxylic acid) is a synthetic derivative of the amino acid lysine. It exerts its antifibrinolytic effect through the reversible blockade of lysine binding sites on plasminogen activator and thus prevents fibrinolysis and breakdown of clot.⁸

Ethamsylate works by increasing capillary endothelial resistance and promoting platelet adhesion. It also inhibits biosynthesis and action of those prostaglandins, which cause platelet disaggregation, vasodilation and increased capillary permeability.⁹

In obstetrics, tranexamic acid is used before and after delivery to reduce bleeding, often with syntocinon and fundal massage. During delivery, when the placenta separates from the uterine wall, a sequence of physiological and haemostatic changes occur that reduces bleeding, cause strong myometrial contractions, increased platelet activity and a massive release of coagulant factors, but there is also a parallel increase in the fibrinolytic activity. The fibrinolytic system is activated after rapid reduction of fibrin and fibrinogen following the removal of placenta and fibrin degradation products are increased because plasminogen

activators catalyse the conversion of plasminogen to plasmin.

Molecular weight of 157.21 g-mol, tranexamic acid can cross the placental barrier. The concentration in cord blood after an intravenous injection of 10 mg per kg to pregnant women about 30 mg per L as high as maternal blood. Unlike other antifibrinolytic agents, TXA is proved to be better drug under its class for various purposes with minimum side effects. Its potency is approximately 10 fold greater than epsilon aminocaproic acid. The plasma protein binding of tranexamic acid is about 3% at therapeutic plasma levels, which is fully bound to plasminogen and bound to serum albumin. The initial volume of distribution is 9 to 12 litres and the concentration of tranexamic acid remains different tissues for about 17 hours and in serum up to 7-8 hours, the overall renal clearance is equal to overall plasma clearance about 110-116 ml/min. with 95% of dose excreted in urine as the unchanged drug. Tranexamic acid is typically administered at a loading dose of 15 mg/kg/hr. The initial elimination half-life of TXA approximately 1 to 1.5 hrs.¹⁰ under normal conditions, fibrinolysis provided an important mechanism to limit propagation of intravascular thrombosis, thus action can take up to 6 to 10 hours in the postpartum period. Contraindication for tranexamic acid is subarachnoid haemorrhage, it may increase cerebral ischaemic complications, hypersensitivity and upper renal tract bleeding.

Ethamsylate is known as Cyclomin, synthetic origin and belongs to sulfonates. The molecular weight of ethamsylate is 263.30, it is weakly acidic drug pharmacokinetics of ethamsylate plasma protein binding is 90%. Renal excretion accounts for unchanged part excretion in urine and plasma half-life is 8 hours.

Dosage of ethamsylate 1 g given intravenously, side effects of this drug is headache, nausea, skin rashes and hypotension. Contraindication for ethamsylate is porphyria.

Aims and Objectives

1. To determine the effect of tranexamic acid, ethamsylate in reducing blood loss during and after C-section.
2. To highlight the use of TXA and ethamsylate in decreasing the incidence of postpartum haemorrhage after C-section.
3. To assess the ability of tranexamic acid and ethamsylate in reducing blood transfusion after C-section.

MATERIALS AND METHODS

A prospective randomised double-blinded study was done to compare the efficacy of tranexamic acid and ethamsylate in reducing the blood loss during and after elective C-Section. After the ethical committee approval and informed consent from the patient, the study was conducted in the Department of Obstetrics and Gynaecology in our hospital during January to June 2017.

It included a total of 90 women selected by simple randomisation from January 2016 - June 2017 who underwent elective LSCS at term between 37 and 40 weeks of gestation and 20 to 30 years, average height of 145 to

160 cm, average body weight of 45 to 65 kgs and normotensive patients.

Exclusion Criteria

Patients with medical and surgical disorders involving heart, liver, brain, kidney and blood disorders, abruption placentae, placenta previa, polyhydramnios, multiple gestation, porphyrias, allergy to tranexa, ethamsylate, severe anaemia and history of thromboembolic disorders were excluded.

Methodology- They were randomly divided into 3 groups of 30 women each, study groups, which included AT who received tranexamic acid and AE who received ethamsylate and control group AN who received normal saline.

Double blinding was done. Both the patient and the analyser were blinded in the study.

Study groups AT and AE, each of them received 1 g of tranexa and ethamsylate, diluted in 10 mL normal saline and administered slowly intravenously over 10 minutes at least 20 mins. before skin incision.

All patients received 10 IU of oxytocin infusion and 10 IU intramuscularly along with uterine massage after delivery.

Calculation of Blood Loss- Blood pressure, pulse rate, respiratory rate and blood loss during and within 2 hours of C-section were noted. After giving skin incision, blood was soaked into pre-weighed 10 x 10 inches towels and entering the amniotic cavity, amniotic fluid sucked up by vacuum. After removal of placenta, bleeding was again taken into account. 24 hours postpartum blood loss was calculated by weighing pre-weighted pads used by the women. Weighing pre-weighted towels soaked into blood and putting them into the following wet weight-dry weight/1.059 (1.05) is constant. Postoperatively, Hb%, haematocrit (PCV) and TRBC of all women checked after 2 hours. All women along with babies checked up to 7 days as it is the usual hospital stay for all post-caesarean patient. TXA reduced the blood loss by 92 milliliters¹¹ and with most frequently reported adverse effect being nausea. Ethamsylate reduced by 89 mL. The bleeding duration was shorter and postoperative PRBC transfusion was less frequent in the both TXA and ethamsylate users.

RESULTS

Total 90 women participated and all LSCS done under spinal anaesthesia. There were no statistically significant difference in subject's characteristics (Table 1) and vitals in all the three groups. The basal haemoglobin concentration was recorded (Table 2). They were similar in respect to obstetrical complications. There was no statistical difference in preoperative systolic blood pressure, haemoglobin, PCV and TRBC of all the three groups. Mean time taken for LSCS was 40 ± 5 minutes for study groups and 45 ± 5 minutes for control group. The intraoperative blood loss was not statistically significant ($p = 0.12$) between both the study groups, but statistically significant from the control group. Even the 2 hours postoperative blood loss was not significant between both the study group, but statistically significant

from the control group ($p < 0.001$). The drop in Hb was significant in between the study groups versus control group (Table 3). Hence, there was statistically significant difference in total blood loss in the control group. There were 17% for

TXA, 15% for ethamsylate reduction of blood loss in study group when compared to control group in postoperative period (Table 4).

Parameter	Tranexa Group (n=30)	Ethamsylate Group (n=30)	Saline Group (n=30)	P value (t test)
Age mean (SD) years	24.60 (1.61)	22.32 (1.52)	24.94 (1.58)	P=0.64
Weight mean (SD) kg	48.36 (2.83)	47.93 (2.59)	48.28 (2.69)	P=0.54
Height mean (SD) cm	153.34 (3.14)	152.56 (3.19)	153 (2.34)	P=0.70
Gestational age mean (SD) wks.	38.65 (1.23)	37.62 (1.13)	38.44 (1.47)	P=0.66

Table 1. Demographic Data $p > 0.01$, Not Significant

Hb Concentration	TXA Group	Ethamsylate Group	Saline Group
7-9	8	9	10
9-10.9	12	12	11
>11	10	9	9

Table 2. Basal Haemoglobin (Hb) Concentration (gm%)

Hb Concentration	TXA Mean (SD)	Ethamsylate Mean (SD)	Saline Group Mean (SD)	P Value
Drop	0.5 (0.15)	0.5 (0.15)	0.9 (0.14)	P < 0.001

Table 3. Drop in Hb Concentration P value < 0.001 is Significant

Comparison of postpartum HE.

Group	Placental Delivery to End of LSCS, Mean (SD) mL	End of LSCS To 2 hrs. Postpartum, Mean (SD) mL	Placental Delivery to 2 hrs. Postpartum, Mean (SD) mL
TXA (sgp)	294.94 (32.8)	71.94 (20.07)	267.02 (51.10)
ETM (sgp)	299.35 (30.32)	73.24 (22.35)	280.39 (53.25)
Saline (cgp)	335.5 (43.5)	129.1 (23.92)	464.6 (66.75)
P value (t test)	P value < 0.001	P value < 0.001	P value < 0.001

Table 4. SGP-Study Group, CGP-Control Group, p Value < 0.001 Significant

DISCUSSION

Obstetric haemorrhages have very high mortality rate, PPH being the most common type. PPH is defined as blood loss of about 500 mL after vaginal delivery, or >1000 mL after C-section. However, these definitions do not take severe anaemia into consideration in whom blood loss as little as 300 to 400 mL would be life-threatening.

There have been a lot of trials using tranexamic acid-woman trial (World Antifibrinolytic Trial), which also assesses thrombotic tendencies of tranexa. Our study was conducted to compare the efficacy of ethamsylate, which is cheaper to tranexa and being less potent causes less thrombotic reactions.

Movafegh A et al¹² demonstrated that 10 mg/kg of TXA 20 minutes before abdominal incision when compared to placebo reduced the mean blood loss for both intraoperative bleeding (262.5 ± 39.6 vs. 404 ± 94.4 mL) and postoperative bleeding (67.1 ± 6.5 vs. 141.0 ± 33.9 mL: $p = 0.001$), respectively during LSCS.

In systematic review with meta-analysis, prophylactic administration of tranexamic acid reduced blood loss and the incidence of severe postpartum haemorrhage. A randomised, double-blind, placebo-controlled study on 660 women showed that intravenous infusion of 1 g TXA significantly reduced blood loss during CS when compared to the placebo control group (499 ± 206.4 mL versus 600.7 ± 215.7 mL, respectively $p < 0.001$). In a mono centre, prospective case control randomised study on 90 anaemic

patients undergoing LSCS with haemoglobin between 7-10 g%, Goswami U et al¹³ found that the reduction in blood loss with IV tranexamic acid 10 mg/kg when compared to the control group were 146.34 ± 56.32 mL and 262 ± 31.5 mL, respectively. Senturk MB et al¹⁴ in a double-blind placebo control study found out that the tranexamic acid reduced intraoperative and postoperative blood loss during LSCS in 223 patients with no complication such as venous thromboembolism, gastrointestinal problems or hypersensitivity.

CONCLUSION

TXA and ethamsylate both are equally effective in reducing intraoperative and postoperative blood loss with minimal side effects. Treatment with ethamsylate is cost effective. It proves to be promising drug for reducing blood loss in obstetrics and reducing the incidence of postoperative blood transfusion. However, further studies or reviews should come up with certain guidelines for its use and clear off the concerns regarding adverse effects.

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