Original Research Article

Effect of injection Tranexamic acid on peri-operative blood loss during Cesarean section

P. Malathi[1*], D. Anupama[2], P. Habitha[3]

[1]Associate Professor, [2]Assistant Professor, [3]Post Graduate
Department of Obstetrics and Gynecology, MGMH, Petkaburz, Hyderabad, India
[*]Corresponding author email: **malathiponnuru@gmail.com**

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Abstract

Background: The achievement of safe child birth by caesarean delivery (CD) was one of the greatest medical advances of the 20th century. Indeed, CD is now the most frequent operation performed, consulting approximately one third of all deliveries annually.
Aim: To evaluate the effect of preoperative administration of Injection tranexamic acid on blood loss during and 2 hrs after elective caesarean delivery.
Materials and methods: This study was a prospective observational study for a period of 15 months; randomized controlled trial was conducted among 200 women scheduled for elective Cesarean delivery.
Results: A comparative study was undertaken to study the effect of inj. TXA on blood loss during and after Cesarean delivery. The mean age in tranexamic group was 23.40±3.06 while in control group was 23.59±3.56. 64% fall in age group 21-25 years. In Gravida Distribution, majority of the patients in both the groups are of Gravida 2 (Group A 65% and Group B 64%). The mean ± SD was 2.17 ± 0.65 in study group and 2.2 ± 0.56 in control group. Comparison of blood loss between two groups**,** intra-operative blood loss was lower in the study group than in the control group 375±69 vs 410±79.9 and is statistically significant. The mean postpartum blood loss was also in the study group than in the control group 52±30 Vs 131±42 and was statistically significant.
Conclusion: Tranexamic acid injection significantly reduces the perioperative blood elective Cesarean section, if given prior to the skin incision, without significant adverse effects**.**

Key words

Tranexamic acid, Postpartum blood loss, Oxytocin.

Introduction

The achievement of safe child birth by Cesarean delivery (CD) was one of the greatest medical advances of the 20th century. Indeed, CD is now the most frequent operation performed in tyhe USA, consulting approximately one third of all deliveries annually [1]. Epidemiologic data report a CD incidence of 20%-30% worldwide, with comparable rates in high-income and low-income countries [2]. The current rate of CD, which is approximately 4-5 folds greater than that of the 1970s, can be attributed to factors such as assumed benefit to the foetus, low maternal risk, social preference, and fear of litigation. Intra partum and early postpartum blood loss are also increased in the conjunction with CD.

Each year, worldwide about 5,30,000 women die from causes related to pregnancy and child birth [3] .Of the deaths 99% are in low and middle income countries. Obstetric haemorrhage is the leading cause of maternal mortality, most occurring in the post partum period. Systemic antifibrinoloytics agents are widely used in surgery to prevent clot breakdown in order to reduce the blood loss. At present there is little reliable evidence from randomised trials on the effectiveness of tranaexamic acid in the treatment of post partum hemorrhage. Post partum hemorrhage is responsible for between 1/4 to 1/3 of the obstetric deaths. The American Congress of Obstetrics and Gynecologist defines PPH is commonly defined as blood loss of ≥ 500 ml after vaginal delivery of baby or ≥ 1000 ml after Cesarean section [4]. However, these thresholds do not take into account pre-existing health status, and blood loss of as little as 200 ml can be life threatening for a woman with severe anaemia or cardiac disease.

Of the 14 million women who have PPH each year, about 2% die with an average interval of 2 to 4 hours from onset of bleeding to death. Although many deaths from PPH occur outside the health care facilities, A significant number occur in hospital, where effective emergency care has the potential to save lives [5]. A Cochrane systematic review published in 2011 examined the use of TXA to prevent PPH. It identified 5 RCTs and included 2 of them in the meta-analysis, which covered a total of 453 women [6]. The authors concluded that the available evidence, although it suggested that TXA decreases postpartum blood loss, was of unclear quality and that further investigation was needed. Tranexamic acid is trans-4-(amino methyl) cyclo hexane carboxylic acid. Molecular formula C8H15 NO2. It is a synthetic analog of amino acid lysine. Used to treat or prevent excessive blood loss during surgery and in various medical conditions or disorders (helping haemostasis). It is an antifibrinolytic that competitively inhibits the activation of plasminogen to plasmin, by binding to specific sites of both plasminogen and plasmin, a molecule responsible for the degradation of fibrin, a protein that forms the frame work of blood clots. Traenexamic acid has roughly 8 times the antifibrinolytic activity of an older analogε-amino caproic acid. Tranexamic acid injection is widely available in the institute where the present study is conducted. There is availability of laboratory facilities and experts of various departments for routine care and critical care, there are ample facilities available for the present study to conduct at the institute Modern Government Maternity Hospital, Petlaburz, Hyderabad. Which is one of the biggest hospital in India where there are good number of samples available.

Materials and methods

This study was a prospective observational study for a period of 15 months, randomized controlled trial was conducted among 200 women scheduled for elective caesarean delivery. Chi-square test was used to compare qualitative

variables between groups and Student t -test was used to compare quantitative variables in parametric data.

Inclusion criteria

Uncomplicated Singleton pregnancy, GA after 37 completed weeks, Primi gravid, Multigravida up to third parity with 1 or 2 previous caesarean sections, without any comorbidities.

Exclusion criteria

They were cases of Unsure due date, Multiple pregnancy, Polyhydramnios Gestational hypertension and pre ecclampsia, Anemia complicating pregnancy, Diabetes mellitus, Antepartum haemorrhage, Preterm labour**,** Fetal distress, Medical and coagulation disorders and Past or present history of DVT.

In subjects who fulfilled the inclusion criteria, history was taken. The patient details, gravida, parity, gestational age are note down. Indication for present caesarean and associated comorbid factors were noted. Clinical evaluation and routine laboratory investigations with particular emphasis on blood indices and coagulation profile were performed. Women with abnormal test results were excluded from the study. Detailed sonographic examination documenting placental localization, estimated fetal weight, and biophysical profile were performed in all cases shortly before operation; women with abnormal sonographic findings were excluded from study. Eligible participants were randomized into two groups. Women in study group (n=100) received Inj. Tranexamic acid 10 mg/kg body weight and Inj. Oxytocin10 U i.m., while women assigned to the control group (n=100) received only Inj. Oxytocin10 U i.m. Inj. Tranexamic acid given 15-20 minutes prior to skin incision before spinal anesthesia. Cesarean delivery was performed under spinal anesthesia, through low transverse skin incision and lower segment Cesarean, 4 senior obstetricians. Obstetricians and operating room staff were not blinded to the allocation. All participants received 10 IU of Oxytocin in 500 ml lactated Ringer solution, which was infused over a period of 30 minutes (i.e.at a rate of 340 mIU per minute) after cord clamping. The time interval between drug administration and delivery of fetus was noted in both study group and control group. The placenta was removed by controlled cord traction after spontaneous separation.

Assesment of blood loss started after uterine incision by Gravimetric method. During operation an isolation suction was used for evacuation of amniotic fluid through a small incision over the uterus, and another one used for collection of blood. Adedicated nurse was responsible for collection of blood and amniotic fluid in 2 separate suction sets, and for weighing surgical swabs and linen before and after operation. Fixed size mops of 20× 10 cm were used in the present study. The weight difference would be nearly the lost blood taking into consideration that 1 gram would be equal to 1 ml of blood. The collected blood in suction bottle would be added to the blood in swabs and clots. A highly accurate digital balance was used for weighing swabs.

The surgeon requested additional uterotonic agents on the basis of clinical findings during surgery. Additional Oxytocin was added to standard oxytocin infusion before Secondary uterotonic agents if intra operative blood loss exceeded 500 ml. Additional oxytocin was considered as additional uterotonic intervention for the purpose of data analysis. Inj .Methylergometrine 0.2 mg IM and Inj15 Methyl prostaglandin F2 α250 µg IM were used as secondary uterotonic agents. Postpartum blood loss during first 2 hours after surgery was assessed by weighing pads and clots. Preoperative and post operative hemoglobins estimated by Sahli's haemoglobin method and hematocrit 1 hour before surgery, 24 hours after surgery by Wintrobes centrifugation method .The neonatal outcome including; APGAR score ,the need for neonatal intensive care unit (NICU) admission and neonatal death were assessed in the two groups. The drug side effects as regards postoperative fever, vomiting and shivering were compared in both groups.

Data were collected and tabulated and statistically analyzed by IBM computer using the Statistical package for the Social Sciences (SPSS version 15).Chi-square test was used to compare qualitative variables between groups and Student t -test was used to compare quantitative variables in parametric data. P value <0.05 was considered statistically significant. Results are presented as mean and standard deviation and the data are normally distributed.

Results

A total of 200 women were recruited for the study. 100 were randomly assigned to injection trenaxamic acid I.V, inj. oxytocin 10 IU, IM and 100 to only inj. Oxytocin 10 IU, IM. All women received allocated intervention, completed follow up and were analysed according to group assignments. A comparative study was undertaken to study the effect of inj. TXA on blood loss during and after Cesarean delivery.

The two groups under consideration are comparable with regard to age distribution. The mean age in tranexamic group was 23.40±3.06 while in control group was 23.59±3.56. 64% fall in age group 21-25 years. Majority of the pateints in both the groups are of Gravida 2 (Group A 65% and Group B 64%). The mean ± SD is 2.17 ± 0.65 in study group and 2.2 ± 0.56 in control group (**Table – 1**).

Table - 1: Demographic distribution.

Age in Years	**Group A Tranexamicacid + oxytocin (n=100)**	**Group B - Oxytocin (n=100)**
≤ 20	21	19
21 – 25	64	63
26-30	14	16
> 30	01	02
Mean ± SD	23.40±3.06	23.59±3.56
Inference	Samples are age matched with P= 0.112	
Gravida		
Primi	9	8
Gravida 2	65	64
Gravida 3	26	28
Mean ± SD	2.17 ± 0.65	2.2 ± 0.56
Number of previous caesarean deliveries		
1	60	64
2	32	28
Mean ± SD	1.24 ± 0.45	1.20 ± 0.44
P value	0.24	

The difference in Hb% before CD and one day after CD was satistically significant. The difference between preoperative and post-operative Hb values 1.34±0.15 and 1.44±0.88 in study and control group respectively with a P value of 0.003 which is statistically significant. This table shows that mean intra-operative blood loss was lower in the study group than in the control group 375±69 vs 410±79.9 and was statistically significant. The mean postpartum blood loss was also in the study group than in the control group 52±30 Vs 131±42 and was statistically significant (**Table – 2**).

Comparison of outcome variables in the study cohort, time until delivery in min was

comparable in both the groups. APGAR at 1 and 5 min was comparable between two groups. These values are not statistically significant. The percentage of cases requiring additional oxytocics was significantly higher in control group than in study group (**Table – 3**).

Table - 2: Comparison of hemoglobin (Hb) between two groups.

Heamoglobin g%/dl	**Group A Tranexamicacid + Oxytocin (Mean±SD)**	**Group B Oxytocin (Mean±SD)**	**P Value**
Before delivery	10.68±1.214	10.80±1.044	0.125
One day after delivery	9.58±1.16	9.50±1.15	0.06
Hb difference	1.34±0.15	1.44±0.88	0.003
Comparision of blood loss between two groups			
Intra operative blood loss	375±69	410±79.9	0.047
2 hrs post operative blood loss	52±30	131±42	0.008

Table - 3: Comparison of outcome variables in study cohort (n=100).

Variable	**Study Group (n=100)**	**Control Group (n=100)**	**P value n=100**
Time until delivery	6.12 ± 0.8	5.91 ± 1.04	0.0001
Apgar at 1 & 5 min	9.2 ± 0.6	9.0 ± 0.8	0.23
NICU admission	6	7	0.77
Intraoperative blood loss	374 ± 69.9	401.5 ± 79.9	0.01
Post partum blood loss per 24h, ml	131 ± 31.8	145 ± 35.6	0.006
Use of additional Oxytocics	8	18	0.03
Hb difference	1.14 ± 0.73	1.44 ± 0.88	0.009
Haematocrit Difference	4.30 ± 2.26	5.25 ± 2.61	0.008
Adverse effects	20	14	0.25

Discussion

The study was carried out at Modern Government Maternity Hospital, Petlaburz, Hyderabad to evaluate the effect of pre operative administration of Inj. Tranexamic acid on blood loss during and after elective caesarean delivery. MGMH is one of the largest maternity hospitals in India conducting more than 21,000 deliveries including 9000 Cesarean sections every year. TXA significantly reduces the uterine blood loss in women with menorrhagia and is recommended for consideration as a treatment in intractable PPH in UK [16].

Tranexamic Acid is widely available to be stored at not greater than 25 ^{0}C and to be protected from freezing. It can be mixed with heparin, should not be added to blood for transfusion or to injections containing penicillin.

Above table shows the Ming- ying Gai, et al. [3] study, the blood loss from placental delivery to end of Cesarean section is not statistically significant but in present study the blood loss from placental delivery to end of LSCS and also from end of LSCS to 2 hrs postpartum is statistically significant [20].

Shahid A, khan A, et al. [4] study Blood loss was collected and measured first from time at placental delivery to the end of LSCS and later from end of LSCS to two hrs post partum. Mean values blood loss were compared using T-test

with significance at p<0.05.The results showed Tranexamic acid significantly reduced the quantity of blood loss from placental delivery to the end of LSCS which was 356.44 ± 143.2 ml in tranexamic acid group Vs 710.22 ± 216.7 ml in the placebo group (p<0.001). It also reduced the quantity of blood loss from the end of LSCS to 2 hours post partum which was 35.68 ± 23.29 ml in tranexamic acid Vs 43.63 ± 28.04 ml in the placebo group (p=0.188) but was not significant statistically (**Table – 4**).

Table – 4: Comparison of present study with other study.

Variable	Study group	Control group	P-Value
Ming –ying Gai et al study [3]			
Blood loss from placental delivery to end of LSCS	322.26± 148.15	358.34± 148.07	0.063
The end of LSCS to 2 hr post partum	42.75± 40.45	74.25± 77.06	0.001
Total blood loss from placental delivery to 2h post	36436 ± 191.48	439.36± 191.48	0.002
Shahid A, Khan A, et al. [4] study			
Blood loss from placental delivery to end of LSCS	356.44 ± 143.2	710.22± 216.7	<0.001
The end of LSCS to 2 hr post partum	35.68 ± 23.29	43.63 ± 28.04	0.188
Total blood loss from placental delivery to 2h post	-	-	-
Nergis taj Ahsan Fidraus, et al. [5]			
Mean blood loss during LSCS	260 ± 11	485± 16	0.003
Ali Movafegh, Laseh Eslamian, et al. [6]			
Blood loss from placental delivery to end of C/S.	262.5 ± 39.6	404.7± 94.4	<0.001
The end of c/s to 2hr post partum	67.1± 6.5	141 ± 33.9	0.001
Jianjun Xu Wei Crao, YingnanJu, et al. [7]			
Blood loss from placental delivery to end of C/S.	379.2±160	441± 189.5	<0.001
The end of c/s to 2 hr post partum	46.6± 42.7	84.7 ± 80.5	0.001
P.S Rashmi, TR Sudhaprabhu das, et al. study [8]			
Mean blood loss from end of LSCS to 2 hrs postpartum	86.5	142	0.001
Gohel Mayur, Patel Purvi, Gupta Ashoo, Desai Pankaj, et al. [9]			
Blood loss from placental delivery to end of C/S.	469	572	<0.001
The end of c/s to 2 hr post partum	75	133	0.001
Present study			
Blood loss from placental delivery to end of LSCS	375ml ±89	410ml ±79.9	0.047
The end of LSCS to 2 hr post partum	52 + 30	131ml + 42	0.062
Total blood loss from placental delivery to 2h post	353.92 + 158.09	430.21 + 196.8	0.0038

In present study mean values of blood loss were compared using t-test with significance at p=0.04.The results showed TXA significantly reduced the quantity of blood loss from placental delivery to end of LSCS which was 375±69 ml in TXA group Vs 410 ±79.9 ml compared to group to whom TXA was not given(0.04).It also reduced the quantity of blood loss from end of LSCS to 2 hrs postpartum which was 52±30 ml in TXA group Vs 131±42 ml in control group(p=0,006)which is statistically significant.

NergisTaj Ahsan Fidraus, et al. [5] study. 60 women received tranexamic acid, and 60 received placebo. Mean blood loss was 260 ± 11 ml Vs 485 ± 16 ml in tranexamic acid Vs the control group (p=0.003). In present study mean values of blood loss was 375±69 ml in TXA

group Vs 410 ±79.9 ml compared to group to whom TXA was not given(0.04).

Ali Movafegh, Laseh Eslamian, et al. [6] study showed, Mean blood loss was significantly less in tranexamic acid group compared with control group for both intra operative bleeding (262.5 ± 39.6 Vs 404.7 ± 94.4 ml) and post op bleeding (67.1 ± 6.5 Vs 141 ± 33.9 ml; p< 0.001) respectively.(6) Oxytocin administration was significantly less in the tranexamic acid group compared with control group (39 ± 5.8 Vs 43 ± 5.4 units ; p=0.001).

In present study the , Mean blood load was significantly less in tranexamic acid group compared with control group for both intra operative bleeding (375 ±69 Vs 410 ± 79.9) and post op bleeding from end of LSCS to 2 hrs postpartum (52 ± 30 Vs131 ± 42 ml ; p= 0.006) respectively. Both the studies were comparable.

Jianjun Xu Wei Crao, YingnanJu, et al. [7] study has the following results- Blood loss in the period between the end of caesarean section and 2 hours post partum was significantly less in (p<0.01) in tranexamic acid group (46.6 ± 42.7) than in control group (84.7 ± 80.2). The quantity of total blood from placental delivery to 2 hours post partum was also significantly reduced (p=0.02) in tranexamic acid group (379.2 ± 160.1) than in control group (441.7 ± 189.5). However, the amount of blood loss in period from placental delivery to in period from placental delivery to end of caesarean section did not differ between tranexamic acid and control group (p=0.17).

PPH stopped in 65 women (75.6 %) in control group and in 81 (92%) in tranexamic acid group (p<0.01).In present study the , Mean blood loss was significantly less in tranexamic acid group compared with control group for both intra operative bleeding (375 ±69 Vs 410 ± 79.9) and post op bleeding (52 ± 30 Vs131 ± 42 ml ; p= 0.006) respectively.

P.S Rashmi, et al. [8], study results showing tranexamic acid significantly reduced the quantity of blood loss from end of LSCS to 2 hours post operation. 86.5 ml in study group Vs 142.7 ml in the control group (p<0.001), it also significantly reduced the quantity of blood loss from placental delivery to two has post partum. No complications or side effects were noted. In present study the, Mean post op bleeding (52 ± 30 Vs131 ± 42 ml ; p= 0.006) is significantly less in TXA group from end of LSCS to 2 hrs postpartum.

Gohel Mayur, Patel Purvi, Gupta Ashoo, Desai Pankaj, et al. [9] Study showed the Tranexamic acid significantly reduced the quantity of blood loss from end of LSCS to post partum. 75.7 ml in study group Vs 133 ml in control group (p=0.001). It also significantly reduced the quantity of blood loss from placenta delivery to 2 hours post partum, 469 ml in study group Vs 572ml in control groups (p=0.003).

In present study mean values of blood loss were compared using t-test with significance at p=0.04. The results showed TXA significantly reduced the quantity of blood loss from placental delivery to end of LSCS which was 375±69 ml in TXA group Vs 410 ±79.9 ml compared to group to whom TXA was not given (0.04). It also reduced the quantity of blood loss from end of LSCS to 2 hrs postpartum which was 52±30 ml in TXA group Vs 131±42 ml in control group (p=0,006) which is statistically significant. In present study also there was reduced quantity of blood loss from end of LSCS to 2 hrs postpartum which was 52±30 ml in TXA group Vs 131±42 ml in control group (p=0,006) which is statistically significant.

Kumkum Gupta, et al. [10] studied effect of tranexamic acid in radical surgeries, the results showed were: the total measured blood loss (576 ± 53 mL) in tranexamic acid group was significantly less than control group (823 ± 74 mL) (P<0.01). The need for blood transfusion was more in the control group. Only two patients in tranexamic acid group required allogeneic

blood transfusion. Intra-operatively, the amount of crystalloid solution used for fluid replacement was comparable between the groups. The prophylactic administration of tranexamic acid has effectively reduced the blood loss and transfusion needs during radical surgery without any adverse effects or complication of thrombosis. A Cochrane review that examined the effectiveness of antifibrinolytic agents in minimizing the need for a blood transfusion found that TXA did not increase the incidence of myocardial infarction, stroke, deep vein thrombosis or pulmonary embolism.

Katharine Ker, research fellow, Phil Edwards, et al. [11] meta analysis 0f 129 trials, totalling 10 488 patients, show that the Tranexamic acid reduced the probability of receiving a blood transfusion by a third (risk ratio 0.62, 95% confidence interval 0.58 to 0.65; P<0.001). This effect remained when the analysis was restricted to trials using adequate allocation concealment (0.68, 0.62 to 0.74; P<0.001). In present study no patient required the blood transfusion as the study has excluded all the high risk cases. Therefore the present study could not give any report regarding the efficacy of tranexamic acid in reducing blood transfusions, however the above coated meta analysis shows there is significant reduction in probability of receiving blood transfusions.

Leili Safdarian, Aida Najafian, Sara Moshfeghi, et al. [12] study result showing: Personal characteristics were similar in both groups and there are no significant differences in age, number of pregnancies and number of child birth and even Hb before surgery between the two groups. Hemoglobin loss in the study group was significantly less than the control group (p <0.001) No patient required blood transfusions. Bleeding from the placental delivery to end of surgery and from the end of surgery to 2 hours after surgery was significantly less in the control group (p <0.001). The present study is also comparable, result show that the difference in Hb % before CD and one day after CD was statistically significant. The difference between preoperative and post Operative Hb values1.34±0.15 and 1.44±0.88 in study and control group respectively with a P value of 0.003 which is statistically significant.

H-Y Wang, S-K Hong, Y Duan, H-M Yin, et al. [13] conducted a meta analysis, the results were showing Total blood loss during and after CS was significantly less in TXA group than in control group (mean difference (MD) −141.61 ml, 95% confidence interval (CI) −207.09 to −76.14, P<0.01). There was a significant reduction in intra-operative and postpartum blood loss in TXA group as compared with control group (MD −143.36 ml, 95% CI −220.38 to −66.35, P<0.01; and MD −38.20 ml, 95% CI −59.27 to −17.12, P<0.01, respectively). Declines in hemoglobin and hematocrit values after CS were both significantly less in TXA group than in control group. The difference of postpartum hemorrhage rate was statistically significant between groups (risk ratio (RR) 0.57, 95% CI 0.37 to 0.89, P=0.01). The need for blood transfusion was significantly less in TXA group than control group (RR 0.23, 95% CI 0.10 to 0.57, P<0.01).(25) ,the present study is also comparable, result show that the difference in Hb% before CD and one day after CD was statistically significant. The difference between preoperative and post Operative Hb values 1.34±0.15 and 1.44±0.88 in study and control group respectively with a P value of 0.003 which is statistically significant.

Novikova N, Hofmeyr G, Cluver C, et al. [14] Cochrane review has the promising results for mean blood loss, results showing were TA decreased blood loss greater than 400 mL or greater than 500 mL and this effect was more apparent with vaginal births. The studies had methodological shortcomings. Blood loss greater than 1000 mL decreased with the use of TA in six trials (2093 women), however, the difference was most obvious in caesarean section (two trials, 1400 women) and not in vaginal birth in which there were few such outcomes (one trial, 439 women).

The results were comparable with present study. Although there is promise in the use of TXA for prevention and treatment of PPH, large, high quality RCTs are necessary before widespread usage can be supported and considered safe for administration. Of note, The World Maternal Antifibrinolytic Trial (WOMAN) trial, which is a large, international randomized placebo controlled study, is currently ongoing at this time to compare the impact of a 1 g dose of TXA at the onset of post-partum bleeding on mortality. The results of this study should provide more evidence about the potential benefits of TXA to the mother. It must be noted that majority of these RCTs included small sample sizes with inadequate power to fully assess the risk of adverse effect.

Conclusion

Tranexamic acid injection significantly reduces the perioperative blood elective Cesarean section, if given prior to the skin incision, without significant adverse effects**.**

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