Research High Lights

Clinical Assessment of the Effect of Intravenous Tranexamic Acid in Decreasing Blood Loss During Elective Cesarean Section

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ABSTRACT

Objective: Determine the effectiveness and protection of tranexamic acid (TXA) in minimizing blood loss before and after cesarean section (CS).

Study Design: A Non-randomized controlled study. In University Hospitals the period from December 2019 to July 2020.

Methodology: This study was conducted on 220 patients attending to labor ward for elective cesarean section. The patients were divided into two groups(study group and control group) 110 women in each. The study group received injection of 1 gm. of TXA while the control group received 10 ml. of normal saline 10 minutes before the surgery. Blood loss was measured by equation calculating the differences between pre- and 24 hrs. post-operative hematocrit values of each patient.

Results: Tranexamic acid significantly reduced the quantity of total blood loss which was 647.93±155.0 ml in the TXA group versus 773.79±141.7 ml in the control group ($p < 0.001$). The proportion of women in the TXA group who had an estimated blood loss >1000 mL was significantly lower than in the control group [2 (1.8%) versus 9 (8.2%), respectively]; and there were no significant differences between both group as regards the need for additional uterotonic agents nor blood transfusion . Furthermore, no episode of thrombosis was reported in the study. No complications or side effects were reported in either group.

Conclusion: Tranexamic acid significantly reduced the amount of total blood loss during cesarean section. Its use was not associated with any side effects or complication like thrombosis. TXA can be used safely and effectively in women undergoing LSCS.

Key Words: Blood loss, cesarean section, tranexamic acid.

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INTRODUCTION

Obstetric hemorrhage remains one of the major determinants of maternal death in both developed and developing countries. Because of its weight as a leading cause of maternal mortality and morbidity, obstetric hemorrhage (ante-partum and post- partum hemorrhages) must be investigated for national guideline development[1,2].

In severe cases , CS may result in major obstetric hemorrhage, hysterectomy, admission to an intensive care unit, or maternal death. Medications, such as oxytocin, misoprostol, prostaglandin F2α, and methyl ergonovine, have been used to control bleeding after CS[3]. Patients requiring blood transfusion face the risk of transfusion reactions and viral infections[4]. As a result, reducing intrapartum and postpartum bleeding in both cesarean section and vaginal delivery patients is very important to reduce the rates of maternal mortality and morbidity[5].

Tranexamic acid decreases post-partum blood loss after vaginal birth and after cesarean section based on two randomized controlled trials (RCTs)[6,7]. In our study we aim to reach the minimal blood loss during elective cesarean section (CS) in order to decrease patients' morbidity by using Tranexamic acid (TXA) injection before operation time.

PATIENTS AND METHODS

This non-randomized controlled study was conducted at University Hospitals in the period from December 2019 to July 2020. This study was conducted on 220 patients attending to labor ward for elective cesarean section. Sample size was calculated using data from previous studies, and Open Epi Version 2, setting the power at 80%, the two-sided confidence interval at 95% . Calculation according to these values, the minimal number of women needed to produce a statistically acceptable figure was 110

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in each group. Therefore, two hundred and twenty women 220 were recruited in our study to be divided in to two groups.

There two groups in our study first group received 1gm tranexamic acid (2 ampules=10 ml) was administered intravenous 10 minutes before skin incision slowly infused (over 5 min). After delivery of the neonate, oxytocin 10 units IV drip was administered. The second group consisted of 110 pregnant females who were subjected to:10 ml. normal saline solution was administered intravenous 10 minutes before skin incision slowly infused (over 5 min). Oxytocin 10 units IV drip was given after delivery of the neonate as a study group.

Inclusion criteria

We include in our study; Pregnant women with singleton living fetus, Completed 37 weeks gestational age or above. We exclude pregnant women with Severe medical and surgical complications involving the heart, liver or kidney, brain disease and blood disorders, Bleeding tendency, known allergy to tranexamic acid, History of thrombo-embolic disorders, pregnancy complications, such as preeclampsia, abnormally situated placenta (detected by U/S), Antepartum hemorrhage, Multiple pregnancies, macrosomia, polyhydramnios, Fetal distress.

Intervention and follow up

We took from every patient Informed consent obtained from the patients; History taking, examination.

A) Clinical observation

1. Vital signs, 2. Maternal and neonatal side effects caused by tranexamic acid such as GIT upsets, visual disturbances, itching, symptoms and signs indicating thrombosis. (Keeping in mind that there is no known antidote for tranexamic acid. In the event of adverse effects, the patient should be treated symptomatically and supportive measures should be instituted as required.

B) Operative procedures

- All CS were done under spinal anaesthesia.
- All CS were done by only three surgeons to avoid the disparity in the procedures and operative time.
- Before surgery, a Foley's catheter is placed to ensure empty bladder during the procedure and urine output can be monitored to help evaluate fluid status.
- Disinfection of surgical site of patient skin with povidine iodine then draping the patient.

C) Laboratory examinations

Complete blood count (CBC) was performed before delivery and 24 hours after cesarean section.

Evaluation of the efficacy and safety of tranexamic acid in Cesarean Section:

Efficacy

1. The quantity of blood loss was measured.
2. The incidence of postpartum hemorrhage was observed.

Safety

1. Vital signs were monitored.
2. General and local reactions caused by tranexamic acid were guarded.

Statistical analysis

Data collected throughout history, basic clinical examination, laboratory investigations and outcome measures coded, entered and analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0) (Statistical Package for the Social Sciences) software for analysis.

RESULTS

In this study two hundred twenty (220) pregnant female undergoing cesarean section were studied ; 110 of them as Tranexamic Acid group and the other 110 as control group to assess the effectiveness of Tranexamic Acid on control blood loss in patients undergoing elective cesarean section.

(Table 1) showed that there was no significant difference between tranexamic and control group with regard the age and the parity as the age of control and tranexamic group were 27.8±4.98 & 27.36±5.9 respectively and multipara represented the majority in both groups (p>0.05).

Table 1: age and parity distribution among studied groups

Characteristics		Control group		Tranexamic acid group		*P*
		N	%	N	%	
Age						
<30		83	75.5	82	74.5	0.86
>30		27	24.5	28	25.5	
Mean ±SD		27.8±4.98		27.36±5.9		0.546
Parity	Multipara	98	89.1	93	84.5	0.31
	PG	12	10.9	17	15.5	

(Table 2) showed non-significant difference between control group and Tranexamic acid group as regard gestational age and weight of patients before cesarean section also showed non-significant difference between groups as regard HR pre operative and 2 hour post operative ;but in comparing HR during Operation in both , it was significantly higher in tranexamic acid group , while at 1 hour post Operative; it was significantly lower. DPB one hour post Operative was significantly lower in tranexamic acid group. there was no significant difference between groups in RR before cesarean section but there were significant differences regard RR during and after cesarean section as tranexamic acid group was significantly lower.

Table 2: comparison between control and tranexamic acid group regard gestational age and weight and vital signs before elective cesarean

Characteristics	Control group N=110	Tranexamic acid group N=110	*P*
Gestational age (GA) in (wks.)	38.5±0.9	38.53±1.57	0.834
Weight (kg.)	75.84±6.04	76.8±5.3	0.195
HR pre operative (B/min.)	84.12±4.4	84.49±3.5	0.501
HR during operation(B/min.)	88.09±11.5	90.87±3.59	0.017*
HR 1 hour post operative(B/min.)	83.99±4.3	81.93±3.5	0.00**
HR 2 hour post operative(B/min.)	85.0±3.7	85.03±8.06	0.966
SBP pre operative (mmHg)	113.5±9.3	114.5±6.9	0.367
DPB pre operative (mmHg)	74.17±7.5	73.87±6.3	0.092
SBP during operation(mmHg)	109.72±8.1	108.95±5.8	0.476
DBP during operation(mmHg)	69.87±9.8	68.54±8.2	0.071
SBP 1 hour post operative(mmHg)	115.74±8.55	114.77±6.88	0.354
DBP 1 hour post operative(mmHg)	78.1±8.7	75.95±9.51	0.01*
SBP 2 hour post operative(mmHg)	109.81±7.61	110.25±4.4	0.091
DBP 2 hour post operative(mmHg)	72.19±7.5	72.22±6.3	0.969
RR pre Operative (Cycle/min.)	18.84±3.4	18.82±3.1	0.221
RR during Operation (Cycle/min.)	22.2±1.49	21.3±1.3	0.00**
RR 1hour post Operative (Cycle/min.)	18.98±1.3	17.83±0.69	0.00**
RR 2hour post Operative (Cycle/min.)	18.07±1.18	17.17±0.58	0.00**

(Table 3) showed that there is no significant difference between groups with regard the pre operative Hematocrit . Blood loss and hematocrit difference were significantly lower in tranexamic acid group but the post operative Hematocrit was significantly higher in tranexamic acid group. With regard the proportion of women who experienced an estimated blood loss >1000mL there was a significant decrease in number of cases who experienced an estimated blood loss >1000mL within the TXA group *p*=0.03.

Table 3: comparison between control and tranexamic acid group with regard hematocrit difference, blood loss and Hematocrit value pre and post cesarean section

Characteristics	Control group N=110	Tranexamic acid group N=110	*P*
Hematocrit pre_operative (%)	37.18±1.59	36.88±1.69	0.110
Hematocrit post _operative (%)	32.63±1.7	33.48±1.72	0.006*
Hematocrit difference (%)	4.49±0.78	3.44±0.97	0.00**
BLOOD OSS (ml.)	773.79±141.7	647.93±155.0	0.00**

No statistically significant differences were found between both groups with regard the additional need of uterotonic agents nor need of blood transfusion.

Table 4 compares outcomes between a control group (n=110) and a Tranexamic Acid (TA) group (n=110). It shows that the Tranexamic Acid group had significantly fewer instances of blood loss exceeding 1000 mL (1.8%) compared to the control group (8.2%), with a statistically significant *P-value* of 0.03. There was no significant difference between the groups in the rates of blood transfusion (1.8% in control vs. 0.9% in TA group; *P*=0.58) or the need for additional uterotonic agents (10.9% in control vs. 9.09% in TA group; *P*=0.684). The table also lists various thromboembolic events (Deep venous thrombosis, Myocardial infarction, Stroke, Renal failure, Pulmonary embolism), but no occurrences were reported in either group for these complications.

Table 5 compares outcomes for newborns from the control group (n=110) and the Tranexamic Acid group (n=110). It shows no statistically significant differences between the two groups regarding Apgar scores at 1 minute (mean 8.23 vs. 8.29, *P*=0.916) or at 5 minutes (mean 9.31 vs. 9.37, *P*=0.741). Similarly, the incidence of an Apgar score less than 7 at 5 minutes was comparable between the control (1.8%) and Tranexamic Acid groups (2.7%), with a *P-value* of 0.67, indicating no significant difference in this neonatal outcome.

Table 4: Comparison of Surgical Outcomes between Groups

Characteristics	Control group n=110	Tranexamic acid group n=110	*P*
Blood loss >1000 mL (n, %)	9 (8.2%)	2 (1.8%)	0.03*
Blood transfusion (n, %)	2(1.8%)	1(0.9%)	0.58
Additional terotonic agent (n, %)	12 (10.9%)	10 (9.09%)	0.684
Thromboembolic events (n, %)			
1. Deep venous thrombosis	-	-	
2. Myocardial infarction	-	-	-
3. Stroke	-	-	
4. Renal failure	-	-	
5. Pulmonary embolism	-	-	

Table 5: Neonatal Findings

Characteristics	Control group n=110	Tranexamic acid group n=110	*P*
Apgar score at 1 min	8.23±1.21	8.29±1.03	0.916
Apgar score at 5 min	9.31±0.69	9.37±0.87	0.741
Apgar score < 7 at 5 min (n, %)	2 (1.8%)	3 (2.7%)	0.67

DISCUSSION

World Maternal Antifibrinolytic Trial (WOMAN) is an ongoing large pragmatic randomized double-blind, placebo controlled trial, among women with a clinical diagnosis of postpartum hemorrhage. This trial will determine reliably the effect of the early administration of TXA on death, hysterectomy and other morbidities (surgical interventions, blood transfusion and risk of non-fatal vascular events), in woman with PPH. The trial is ongoing and expected to end in December 2015 aiming to recruit 15,000 women with postpartum bleeding from hospitals in Africa, Asia, South America and Europe[8].

The aim of this study was to assess the effectiveness and safety of intravenous administration of tranexamic acid to reduce blood loss in elective cesarean section.

This study was conducted on 220 patients divided into study group = 110& control group = 110 (all are elective CS, gestational age ≥37 weeks and all received spinal anesthesia).

The study Group was subjected to: injection of 1 gm TXA IV 10 minutes before the skin incision slowly infused over 5 min. After delivery of the neonate, 10 units of Oxytocin were given by IV drip over a 500 ml of lactated Ringer's solution.

The control group was subjected to: 10 ml. saline administered intravenous 10 minutes before skin incision slowly infused (over 5 min). 10 units of Oxytocin were given by IV drip after delivery of the neonate as a study group.

In the current study we found that the total blood loss (TBL) difference was significantly lower in tranexamic acid group 647.93±155.0 while it was 773.79±141.7 in control group with *P value* < 0.01.This means that TXA can reduce TBL by 125 ml. (16.3%).

This results were consistent with those reported by Bhatia and her colleagues in 2015[11] where they found that TXA can reduce the TBL during CS by 20% (about 100 ml.), same results were concluded by[12].

Other four studies found a higher significant difference between both groups in the amount of TBL and the proportion of preserved amount of blood in cases of TXA group[13,14,9,15].

With regard to the incidence of PPH ; we concluded that there was a significant decrease of PPH incidence within the TXA group[two cases (1.8%)] versus [nine cases (8.2%)] in control group, with *p value* =0.03. So TXA can reduce the incidence of PPH by 6.4%.

Same results were concluded by Maged *et al*. (2015) as only six cases of PPH were reported within the control group (6%) while no PPH cases were reported within TXA group[15].

Other four trials reported a higher decrease in PPH incidence. We found that these trials used an additional regimen of uterotonics as for example; a higher dose of oxytocin (35 iu) in the trial done by Shahid *et al* 2013[13],or a dose of 0.2 mg methyl ergometrine used in Bhatia *et al*.(2015)[11] and Gobber *et al*.(2014)[12] trials. Higher dose (0.4 mg) of methyl ergometrine was used in trial done by Shahid *et al* (2013). Beside that Bhatia *et al*. (2015), Gobber *et al*. (2014) and Shahid *et al* (2013) measured TBL only for 2 hrs. post CS while Yehia *et al*. (2014) measured TBL for 6 hrs. post CS[11,12,13,6].

In 2013; Abdel-Aleem *et al*. reported that there was no difference in PPH incidence between both groups (only 2 cases in each group)[14].

In our study, two cases (1.8%) in control group needed blood transfusion while only one case (0.9%) within the TXA group, but this was not of significant value. In 2014; Ramani *et al*. reported that with regard to the need of blood transfusion between both groups ; a significant decrease in number of cases needed blood transfusion within TXA group [six cases (10%) vs two cases (3.3%) in control and TXA groups respectively]. This significant difference might be due to that they did not exclude anemic patients from their trial[16].

In our trial we found that the 24 hrs. post-operative hematocrit was significantly higher within the TXA group than control one (33.48 ±1.72 % vs 32.63 ±1.7% respectively) with *p value* = 0.006. As regards the drop in hematocrit from pre operation to 24 hrs. post operation, there was significant lower drop within TXA group than control one (3.44 0.97% vs 4.49 0.78% respectively) with *p value* less than 0.001.

These results were supported by those reported by Yehia *et al*. (2014) as post-operative hematocrit was significantly higher within the TXA group (30.2 ± 6.6%) compared to control (29.2 ± 2.8%), *P*<0.05[6].

Güngordük *et al*. (2011) reported a lower significant difference in the postoperative hematocrit between both groups (30.1±1.0% vs 30.7±1.5% in control and TXA groups respectively) with *p* <0.001. they used a higher dose (35 iu) of oxytocin[10].

A higher significant difference in the postoperative hematocrit between both groups was reported by Shahid *et al* (2013)as it was higher within TXA group (33.08 ±1.80%) compared to control (30.53 ±3.28%), *P*<0.001[13].

As regards the vital signs difference between both groups we concluded that there was a significant decrease in respiratory rate (RR) during Operation within TXA group (22.2±1.49 breaths/min vs 21.3±1.3 breaths/min in control and TXA groups respectively) *P*<0.001. This result was consistent with that reported by Shahid *et al* (2013) (18.72 ±0.81 breaths/min vs 18.05 ±0.517 breaths/min in control and TXA groups respectively) *P*<0.001[13].

The postoperative RR was significantly lower within TXA group in both 1hr. and 2hrs. post CS; RR 1 hr. post CS (18.98±1.3 breaths/min vs 17.83±0.69 breaths/min in control and TXA groups respectively) *P*<0.001. While RR 2hrs. post CS (18.07±1.18 breaths/min vs 17.17±0.58 breaths/min in control and TXA groups respectively) *P*<0.001. These results were consistent with that reported by Abdel-Aleem *et al*. (2013) as the post operative RR was significantly lower within TXA group (20.03 ±1.67 breaths/min vs19.01 ±1.35 breaths/min in control and TXA groups respectively) *P*<0.001[14].

Also , heart rate (HR) during operation was significantly higher within TXA group. It was (88.09±11.5 bpm vs 90.87±3.59 bpm in control and TXA groups respectively) *P*= 0.017.

In relation to HR 1 hr. post CS we found that it was significantly lower within TXA group (83.99±4.3 bpm vs 81.93±3.5 bpm in control and TXA groups respectively) P<0.001. This result was consistent with that reported by Abdel-Aleem *et al*. (2013) as the post operative HR was significantly lower within TXA group (97.81±4.64 bpm vs 91.37 ±5.82 bpm in control and TXA groups respectively) *P*<0.0001[14].

Finally, the diastolic blood pressure (DBP) 1 hr. post CS was significantly lower within TXA group (78.1±8.7 mm Hg vs 75.95±9.51 mm Hg in control and TXA groups respectively) *P* = 0.01 .

The following items may explain the previously mentioned significant difference with regards the vital signs between both groups :

- TXA can cause a decline in blood pressure and rise the pulse even if injected slowly; but it seems to be for some duration as it was evidenced by loss of significant difference between both groups as regards HR & DBP 2 hrs. post CS.
- The concomitant use of oxytocin in the study which carries the same effect on blood pressure and HR.
- Spinal anaesthesia which was offered to all patients involved in our study has a lowering effect on both HR and blood pressure.

In our study ,we did not notice any of side effects that are concerned with the use of TXA in the study group. Some previous trials Güngordük *et al*. (2011), Gobber *et al*. (2014) and Bhatia *et al*. (2015) reported some of mild side effects such as nausea, vomiting ,diarrhoea and visual disturbances occurred frequently within TXA group but without any significance[10,12,11].

Abdel-Aleem *et al*. (2013) reported that only mild side effects such as nausea, vomiting and headache were significantly higher within TXA group (277 cases (74.3%) vs195 cases (53.1%) with *P* =0.0001[14].

Two studies used a relatively large sample size Abdel-Aleem *et al*. (2013) (Study group (n=373) and Control group (n=367)) and Güngordük *et al*. (2011) (330 patients in each group) ; this large sample size might be the reason to highlight such side effects[14,10].

No episodes of thrombosis were reported in our study as there was no deep venous thrombosis, myocardial infarction , pulmonary embolism stroke nor renal cortical necrosis neither within TXA group nor control one. same result was reported by Yehia *et al*. (2014), Gobber *et al*. (2014), Maged *et al*. (2015) and Bhatia *et al*. (2015) [6,12,15,11].

With regards the early neonatal outcome in our study we found that there was no significant differences were observed between both groups in the neonatal outcome regarding the one and 5 minutes Apgar scores.

CONCLUSION

Tranexamic acid is valuable and significantly reducing the quantity of blood loss during and after CS but further studies are needed to exclude any short or long term effects on the mother or the fetus.

CONFLICT OF INTERESTS

There are no conflicts of interest.

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