Zagazig University Medical Journal
www.zumj.journals.ekb.eg

July.2021 Volume 27 Issue 4

Manuscript ID ZUMJ-1909-1512 (R3)

DOI 10.21608/zumj.2019.16829.1512

ORIGINAL ARTICLE

Clinical outcomes of Tranexamic acid administration in Elective Cesarean Delivery :-Intra and post operative effects

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Conflict of Interest : Nil

Financial Disclosures : governmental, Faculty of medicine Zagazig university

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Submit Date	2019-09-10
Revise Date	2019-10-14
Accept Date	2019-10-18

ABSTRACT

Background: we hoped to see efficacy of tranexamic acid (TA) on reducing blood loss during elective cesarean delivery and its outcomes intra and postoperatively .**Patient and Methods:** We carried out a randomized, double-blind, placebo-controlled study over 156 females who underwent elective CS. patients were randomly selected to receive an intravenous infusion of TA (1 g/10 mL in 100 mL of lactated ringer before surgery. The primary outcome was estimated blood loss following CS. No demographic difference was observed between sets. **Results:** mean estimated blood loss was significantly lower in females treated with TA in comparison with females in control set (389.75±187.6 ml versus 724.45±214.5 ml, respectively; p<0.001), and percentage of females in TA set who had an estimated blood loss >1000 ml was significantly lower than in control set 3 [3.8%] versus 14 [17.9%], respectively. TA significantly reduced the need for additional uterotonics, females in control set versus TA set 8 [10.3%] versus 3 [3.8%], respectively. **Conclusion:** Maternal outcomes in TA set is better than control set , decrease the incidence of intra-operative atony , minor ooze and need for drain ,also decreased hospital stay significantly, Protected patients from hazards of blood transfusion , reduce incidence of atonic postpartum which in sever cases may lead to hysterectomy , maternal morbidity and mortality. No incidence of thromboembolic events .
fetal outcomes did not differ significantly.
Our results suggest that TA can be used safely and effectively to reduce Bleeding during CS.

Keywords: Tranexamic acid, cesarean delivery,clinical outcomes, bl00d lost, randomized control trial

INTRODUCTION

Conception and delivery are considered as normal physiological phenomena in ladies. Approximately, 10% of deliveries are considered as high risk, some of which may require Cesarean section (CS). Cesarean section is normally performed when a vaginal delivery would put the mother and baby's life at risk but sometimes it is also performed on request. [**1**].

The Cesarean delivery rate in the Middle East is <15% in the majority of the countries, although higher rates have been reported in Egypt , The rate of CS rise from 20% in 2005 to 52 % in 2015 [**2**].

The hematocrit falls by 10% and blood transfusion is required in 6% of women

undergoing Cesarean delivery compared with 4% of women who have a vaginal birth. Numerous methods for performing Cesarean section (CS) exit: the aim is a safe delivery for the infant with minimum maternal morbidity. Operative morbidity includes hemorrhage, anemia, and blood transfusion. And the risks associated with receiving donor blood products [**3**].

Cesarean section may result in major obstetric hemorrhage, hysterectomy, admission to an intensive care unit and maternal death. Medications, such as oxytocin, misoprostol, prostaglandin F2a, and methyl ergonovine, have been used to control bleeding after CS [**4**].

But still the postpartum hemorrhage remaining a leading cause of maternal mortality, especially in developing countries [**5**].

In order to reduce maternal mortality and morbidity caused by bleeding, it is important to reduce amount of bleeding during and after Cesarean section [**6**].

Tranexamic acid (TA) is a synthetic derivative of the amino acid lysine, which is an anti fibrin lytic that reversibly inhibits the activation of plasminogen. Thus inhibiting fibrinolysis and reducing bleeding. tranexamic acid may enhance effectiveness of the patient's own haemostatic mechanism [**7**].

Tranexamic acid is widely used in the field of obstetric. Both antepartum and postpartum hemorrhage are being treated by TA extensively. Although tranexamic acid crosses the placenta, no mutagenic activity or harmful effects of tranexamic acid on the fetus have been reported and animal reproduction studies have shown no teratogenic affects. Tranexamic acid has been well tolerated and has not been associated with a prejudicial effect on the delivery of healthy children [**8**].

PATIENTS AND METHODS

The current study was conducted at Department of Obstetrics and Gynecology in Zagazig University Maternity Hospitals, from March 2018 to March 2019 , A written informed consent was obtained from all participants and the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The work has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration on Helsinki)for studies involving humans.

Subjects included in the study:

Inclusion criteria:

Maternal age: 18-40 years old , Term pregnancy (37 -42weeks),Singleton pregnancy and Elective cesarean sections. Indication for elective sections were previous history of Cesarean delivery, contracted pelvis , abnormal presentation , macrosomic baby , 1ry infertility and past date not in labor (obst. indication).

Exclusion criteria:

Major maternal medical problem (involving heart, liver, kidney disease) ,Patient with bleeding tendency (hemophillia, ITP,….etc) , Patient with high risk of thrombo-embolism , Known allergy to tranexamic acid , Antepartum hemorrhage , Twin pregnancy , Polyhydraminos and Operative Trauma during CS as extended uterine incision, uterine artery injury, and extensive varicosities over lower uterine segment.

The women were divided into two sets using a random sample technique.

Set I (The study set):

This set consists of 78 pregnant females who were subjected to:

A dose of 1gm of tranexamic acid in 100 ml lactated ringer before giving Spinal anesthesia by slow intravenous injection over 5 minutes. [**4**]**.** After delivery of neonate, 10 IU of oxytocin (syntocinon®, Novartis, Egypt) in 500mL Lactated Ringer's solution.

Set II (The control set):

This set consists of 78 pregnant females in whom10 IU of oxytocin in 500mL Lactated Ringer's solution, was given after delivery of neonate.

Calculation of the quantity of blood loss:

The Estimated blood loss was estimated by using an equation depending on hematocrite levels.

$$\text{Estimated blood loss} = \text{EBV} \times \frac{\text{Preop hematocrit} - \text{Postop hematocrit}}{\text{Preop hematocrit}}$$

Where EBV (estimated blood volume) in ml =the women's weight in kg×85. Blood loss

>1000 mL during the procedure was defined as excessive bleeding. [**4**].

Statistical Analysis:

Data were analyzed using microsoft excel and statistical program for social science (SPSS) version 20.0. The Quantitative data were expressed as mean + standard deviation (SD). Qualitative data were expressed as number and percentage.

The following tests were done:

Independent T- test was used to compare between two quantitative independent groups .Probability (p-value) ,P-value <0.05 was considered significant , P-value<0.001 was considered as highly significant.Chi square test used to test the difference and association of qualitative variable. The Mean and The Standard Deviation (SD).

RESULTS

Table (1): Shows that HB_Postoperative is higher in tranexamic set but not significantly. HCT_Postoperative significantly higher in tranexamic set, HB and HCT difference are significantly higher in Control set.

Table (2): Illustrates that Blood loss is significantly higher in Control set.

Table (3): Demonstrate the intraoperative and postoperative outcomes of the two sets , the Control set is significantly higher as regard blood transfusion and hospital stay more than one day. The need for drain and ecobolics used were higher in Control but not significantly different.

Table (4) : No significant difference regarding the indication for cs in both sets

Table (5): No significant difference between the anemic patients among the two sets.

Table (6) : This table shows comparison between the outcomes of anemic subgroups in TA set and Control Set , Anemic patients in TA set is significantly better regarding the postoperarive HB , HCT are higher with less blood loss , faster postoperative recovery with no need for blood transfusion and less hospital stay.

RESULTS

Table (1): Distribution of HB & HCT pre and post operative between studied set

	Tranexamic set (N=78)	Control set (N=78)	T	P
HB_Preoperative	11.32±1.05	11.64±1.39	-1.623	0.107
HB_Postoperative	10.79±1.02	10.35±1.18	1.956	0.053
HB difference	0.75±0.31	1.17±0.42	-2.928	0.004*
HCT_Preoperative	33.52±2.98	33.97±3.21	-0.913	0.362
HCT_Postoperative	31.28±2.92	30.25±3.45	2.006	0.047*
HCT difference	2.34±0.78	3.72±1.18	-4.985	0.00**

Table (2): Blood loss distribution between studied sets

			Tranexamic set (N=78)	Control set (N=78)	T	P
EBL (ml)			389.75±187.6	724.45±214.5	-7.052	0.00**
EBL	<1000 ml	N	75	64	7.98	0.005*
		%	96.2%	82.1%		
	>1000 ml	N	3	14		
		%	3.8%	17.9%		
Total		N	78	78		
		%	100.0%	100.0%		

Table (3): Maternal outcomes as regard Need for blood transfusion, drain or ecobolics and hospital stay distribution

		Set		Total	X^2	P
		Tranexamic set	Control set			
Need for Blood Transfusion	N	0	4	4	4.1	0.043*
	%	0.0%	5.1%	2.6%		
Need for Drain intraoperative	N	0	3	3	3.05	0.08
	%	0.0%	3.8%	1.9%		
Need for added Ecobolics	N	3	8	11	2.44	0.11
	%	3.8%	10.3%	7.1%		
Hospital stay more than 24 H	N	0	8	8	8.43	0.004*
	%	0.0%	10.3%	5.1%		
Total	N	78	78	156		
	%	100.0%	100.0%	100.0%		

Table (4): Indication of CS distribution in both set

			Set		Total	X2	P
			Tranexamic set	Control set			
Previous CS		N	59	59	118		
		%	75.6%	75.6%	75.6%		
1st CS	CPD	N	5	6	11	0.1	0.74
		%	6.4%	7.7%	7%		
	Breech	N	5	4	9	0.14	0.7
		%	6.4%	5.1%	5.8%		
	1ry infertility	N	4	5	9	0.14	0.7
		%	5.1%	6.4%	5.8%		
	Macrosomia	N	5	4	9	0.14	0.7
		%	6.4%	5.1%	5.8%		
	Total	N	78	78	156		
		%	100.0%	100.0%	100.0%		

Table (5): Anemia (Hb<11gm/dl) before operation distribution between studied sets

			Set		Total	X2	P
			TXA	Control			
Anemia	No	N	53	54	107	0.03	0.86
		%	67.9%	69.2%	68.6%		
	Yes	N	25	24	49		
		%	32.1%	30.8%	31.4%		
Total		N	78	78	156		
		%	100.0%	100.0%	100.0%		

Table (6): Comparison between anemic only among studied sets

			Tranexamic set (N=25)	Control set (N=24)	t/X2	P
HB_Preoperative			10.15±0.55	10.26±0.51	-0.700	0.488
HB_Postoperative			9.59±0.59	9.19±0.79	1.970	0.055
HB difference			0.55±0.16	1.06±0.24	-3.788	<0.001**
HCT_Preoperative			30.66±2.06	30.82±2.24	-0.264	0.793
HCT_Postoperative			28.44±1.64	27.51±2.23	1.682	0.099
HCT difference			2.20±0.425	3.322±0.95	1.926	0.053
EBL (ml)			420.8±118.3	763.02±224.6	-4.980	<0.001**
EBL	<1000 ml	N	25	20	4.53	0.03*
		%	100.0%	83.3%		
	>1000 ml	N	0	4		
		%	0.0%	16.7%		
Need for BL_Transfusion		N	0	3	3.29	0.068
		%	0.0%	12.5%		
Hospital stay more than 24hr		N	0	3	3.29	0.068
		%	0.0%	12.5%		
Need for Drain		N	0	1	1.06	0.32
		%	0.0%	4.2%		
Total		N	25	24		
		%	100.0%	100.0%		

DISCUSSION

The CBC was done before procedure and 24 h after procedure. The mean preoperative HB in studied sets is statistically not different . But post operative HB is higher in TA set than Control set. Control set had HB difference significantly higher than TA set, 1.17 in control set and 0.75 in TA set. Also, HCT preoperative between studied sets wasn't statistically different, but post operative HCT was significantly lower in Control set than TA set. The HCT difference between pre and post operative was significantly higher in Control set than TA set, 3.72 in control set and 2.34 in TA set.

In agreement with our study, a recent study which was performed on 120 women undergoing Cesarean section. They were allocated to either study or control set. TA was given prior to surgery in study set in addition to the routine care (10 units of oxytocin added to the intravenous drip soon after baby delivery) whereas, the control set had routine care only. HB before and after surgery was estimated and the percentage of difference was compared. The study showed that there was significant difference in the percentage of fall in Hemoglobin between the two sets. 60% of subjects in control set had >500 ml of blood loss, whereas, only 3.33% of subjects in study set had increased bleeding. 38.9% of subjects in control set had >10% difference in pre and post-operative Hemoglobin whereas it is only 9.3% in the study set. There were no immediate post-operative complications to the mother and neonate. [**9**].

Another study which was done in india in 2016 over 100 women agree with our study as the difference between preoperative and postoperative HB was significantly less in the study set than the control set 0.26±0.22 versus 0.99±0.8 (P<0.001). [**10**].

Another study was done in 2016 got higher results than our study regarding postoperative HB, this may be due to that he used a higher dose of TA preoperarative. The study was done on 169 patients who subjected to elective CS. Study set include 84 patients who received 2 gm Tranexamic acid before induction of anesthesia plus 10 u oxytocin. The control set received only10 u oxytocin. The 24 hours post-operative hemoglobin was significantly higher in study set (10.68±0.9 mg/dl) compared to control set (8.2±0.7 mg/dl). Also found that 24 hours post-operative hematocrit value was

significantly higher in study set (37.63±5.4) compared to control (31.19±2.48). [**11**]**.**

Another study found that Hemoglobin decreased slightly after Cesarean section in both sets, though not statistically significant and Hemoglobin 24 hours after Cesarean section was significantly greater in the tranexamic set than the control set (12.57 ± 1.33 mg/dL in the tranexamic set and 11.74 ± 1.14 mg/dL in the control set, P = 0.002). [**12**]**.**

In a comparable study which was done in 2014 , found that there was no significant difference regarding pre-operative Hemoglobin and pre-operative hematocrit value, but the 24 hours post-operative Hemoglobin was significantly higher in study set (11.2 mg/dL) compared to control set (9.6 mg/dL) (P<0.05). [**13**]**.**

Similar results have been observed in research conducted on 101 patients (study set) and 122 patients (control set) (primigravirda or multipara at any gestational age, prepared for elective or urgent Cesarean section, they found TA reduced intra-operative and post- operative blood loss. It was observed that the mean difference between the pre- and post procedure Hb values was 1.11±0.62 mg/dL in study set and 1.27±0.66 mg/dL in control set. There was a significant difference (p= 0.034). [**14**]**.**

The study which was done in 2011 on 660 patients which were divided into two sets (TA = 330) and (placebo=330) reported that post operative HB is significantly higher in TA set 10gm/dl while in placebo set was 9 gm/dl , also HB difference in control set is significantly higher than TA set which similar to our study . but a lower significant difference in the postoperative hematocrit between both sets (30.1 ±1.0% vs 30.7±1.5% in control and TA sets respectively) with p <0.001. They used a higher dose (35 iu) of oxytocin. [**4**]

The main goal of our study was to see the efficacy of TA in reducing blood loss during cesarean section. In our study Blood loss is significantly higher in control set 724 ml while in TA set 389 ml.

In a comparable study agreeing with our study done in 2016 , which found that mean estimated blood loss and the proportion of women who experienced an estimated blood loss > 500 ml were significantly lower in TA set than the Placebo set (TA =359.13 +- 75 , Placebo=479.87+-87 , P value<0.0001)**.** [**15**]**.**

Another study showed that mean estimated blood loss was significantly higher in the placebo set (700.3 ±143.9mL) than in the tranexamic acid set (459.4±75.4 mL). So, TA can reduce the amount of TBL by 240 ml (34%). [**16**]**.**

Also similar results was reported in china, giving tranexamic acid 10 min before skin incision. The intervention led to less bleeding 2 h post-operatively, 39 ml in the study set versus 71 ml in the control set (p = 0.02). [**17**].

In agreement with our study,A randomized, double-blind placebo controlled study , 660 women were included and prepared for elective CS , patients received an intravenous infusion of either TA 1g/10 mL in 20mL of 5% glucose in the study set (n=330) or 30 mL 50 glucose in the placebo set (n=330) prior to surgery. The mean estimated blood was significantly lower in TA set compared with the placebo set (499.92±6.4 mL versus 600.72±15.7 mL, respectively; p<0.001). [**4**]**.**

In this study 1000 ml blood loss or more were defined as excessive blood loss and postpartum hemorrhage. In the study set , TA reduced significantly incidence of excessive blood loss and 1ry PPH. Only 3 patients in TA set versus 14 patients in Control set

In a comparable study which focused on blood loss >1000 ml, and defined it PPH, they were six women, all in the placebo set, experienced an EBL of more than 1000 mL. Only 12% of women in the tranexamic acid set had an EBL of 500–1000 mL compared with 94% of women in the placebo set. by [**16**]

The current study showed better maternal outcome in TA set than control set , decrease the incidence of intraoopperative atony , minor ooze and need for drain ,also decreased the hospital stay significantly, Protected patients from hazards of blood transfusion It also reduce incidence of PPH, maternal morbiditiy and mortality, hospital stay, atonic postpartum which in sever cases which may lead to hysterectomy.

In agreement with this study a recent study done between 2010 and 2016 over 193 hospitals among 23 countries. 20060 women were enrolled and randomly assigned to receive

tranexamic acid (n=10051) or placebo (n=10009), of whom 10036 and 9985, respectively, were included in the analysis. Death due to bleeding was significantly reduced in women given tranexamic acid (155 of 10036 patients vs 191 of 9985 in the placebo set, especially in women given treatment within 3 h of giving birth 89 in the tranexamic acid set vs 127 in the placebo set significantly. [**18**]**.**

There were no side effects (allergy or thromboembolic events) occurred among TA set. Also no side effects occured in other studies. [**9, 10**]**.**

CONCLUSION

Tranexamic acid is a good option to reduce the amount of blood loss during and after CS that can be used routinely in CS due its low incidence of side effects and complications. Further studies are needed to exclude any long term effects on the mother or the fetus. Our study demonstrated better maternal outcomes as regard the need for blood transfusion, hospital stay and faster postoperative recovery.

RECOMMENDATIONS

Its srongly recommended further studies should be implemented on larger sample size .also should be carried on anaemic women , women risky for PPH , vaginal delivery patients and urgent CS in order to clearly demonstrate the efficacy of TA in these particular subsets.

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How to Cite

abdel aal, A., diab, A., nossair, W., alkudousy, M. Clinical outcomes of Tranexamic acid administration in Elective Cesarean Delivery :-Intra and post operative effects. *Zagazig University Medical Journal*, 2021; (700-706): -. doi: 10.21608/zumj.2019.16829.1512