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Effect of Tranexamic Acid in Patients with Traumatic Brain Injury

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ABSTRACT

Background: Traumatic brain injury (TBI) is a leading cause of death and disability. Intracranial hemorrhage secondary to TBI is associated with a high risk of coagulopathy and progress of intracranial hemorrhage (ICH). The hemostatic drug tranexamic acid (TXA) with anti-fibrinolytic activity is usually used in patients with trauma to reduce hematoma size. It has been considered a possible therapy to improve the clinical outcome in patients with TBI.

Objective: To evaluate the effect of tranexamic acid on the volume of intracranial bleeding in patients with TBI admitted to Critical Care Unit at Menoufia University Hospital.

Patients and methods: A prospective randomized placebo-controlled double blinded study in the Critical Care Unit, Menoufia University hospitals, through one year from January 2020 to January 2021. The study was carried out on 40 patients with TBI with Glasgow Coma Scale (GCS) of 4 to 12. They had a computerized tomography (CT) brain scan within 8 hours of injury and in whom there was no indication for immediate surgical intervention. We randomly assigned (1:1) patients to receive tranexamic acid (loading dose 1 g over 10 min then infusion of 1 g over 8 hours) or matching placebo.

Results: There was statistically significant reduction in the volume of ICH after 48 hours ($p = 0.021$) in TXA group than in placebo group. While in placebo group, there was high statistically significant increase in volume of ICH after 48 hours compared to on admission. Moreover, TXA reduced the need of blood transfusion, surgical intervention and the incidence of complications with no evidence of increased risk of thromboembolic events.

Conclusion: TXA may reduce the volume of ICH in patients with TBI with no evidence of increased risk of thromboembolic events.

Keywords: Tranexamic acid, Traumatic brain injury.

INTRODUCTION

Trauma is a time-sensitive condition. During the first hours of trauma management, early assessment, resuscitation, and definitive care are very important to decrease disability and mortality [(1)].

Traumatic brain injury (TBI) is a major cause of death and disability worldwide, especially in children and young adults and represents a major social, economic, and health problem [(2)]. Traumatic brain injury (TBI) is commonly accompanied by intracranial bleeding, which occurs in 25% to 45%, 3% to 12% and 0.2% of severe, moderate, and mild TBI cases respectively [(3)]. In patients with TBI, repeated CT scanning has found that intracranial bleeds can develop or expand in the 24 hours after injury and that larger bleeds have a worse prognosis. Delayed enlargement of traumatic intraparenchymal contusions and hematomas is the most common cause of clinical deterioration and death in patients who had a lucid interval after TBI [(4)].

Tranexamic acid (TXA) is a potent anti-fibrinolytic agent that exerts its effect by blocking lysine-binding sites on plasminogen molecules and has the potential to enhance the effectiveness of the patient's own hemostatic mechanisms. Consequently, clot breakdown is inhibited, and excessive or recurrent bleeding is reduced. TXA may be commonly used in surgery to reduce blood loss [(5)].

TXA also has an excellent safety profile and has been shown to be cost-effective. Because of the mechanistic potential for TXA to decrease secondary brain injury, it has been considered as a possible therapy to clinically improve outcomes in patients with TBI by reducing systemic blood loss and hypotension [(6)]. The aim of this work was to evaluate the effect of tranexamic acid on volume changes of intracranial bleeding in patients with TBI.

PATIENTS AND METHODS

This was a prospective randomized placebo-controlled double blinded study that was carried out on 40 patients with TBI. They were admitted at Menoufia University Hospital through one year from January 2020 to January 2021. According to a sealed envelope random allocation, patients were randomized into two groups: tranexamic group and placebo group (20 patients each).

Inclusion Criteria:

Adult patients (>16-year-old) with TBI with Glasgow Coma Scale (GCS) score of 4-12 who had a CT brain scan performed within eight hours of injury.

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Exclusion criteria:

GCS less than 4 or bilateral unreactive pupils at admission, unknown onset of injury, need for immediate surgical intervention, major extracranial bleeding, cerebral infarction, edema or midline shift, hereditary or acquired coagulopathy, platelet count is less than 100,000/mm^3 or international normalized ratio (INR) prolonged more than 1.5 times normal value, serum creatinine more than 2.0 mg/dl, pregnancy, history of current evidence suggestive of venous or arterial thrombotic events as deep vein thrombosis (DVT) or pulmonary embolism and history of hypersensitivity to TXA.

Intervention:

The patients fulfilling the inclusion criteria were divided equally into tranexamic and control groups (20 patients each). Participants and study staff were masked to allocation. Tranexamic group patients received a loading dose of 1 g tranexamic acid infused over 10 minutes, followed by an intravenous infusion of 1 g over 8 hrs.

While, control group received 0.9% normal saline in the same order. Treatments protocols and care were routinely done for all patients. Data were recorded in the checklist by interview and patients' charts. CT brain scans for each participant were obtained, one before randomization and repeated after 24 and 48 hrs.

Study outcomes:

The primary outcome was the effect of TXA in the volume of intracranial hemorrhage (ICH) in patients with TBI. The secondary outcomes were to evaluate worsening of Glasgow coma scale and need for surgical intervention and blood transfusion with the use of tranexamic acid in patients with TBI.

Sample size:

The expansion of ICH as the primary outcome at 48 h after admission was measured by brain CT scan. We estimated a 60% rate of ICH growth in placebo patients, according to the previous studies (Abolfazl Jokar). We planned to randomize 40 patients, 20 to each group. This study would have about 80% power at the 0.05 level of significance (two-sided test) to distinguish a significant difference of 30% in the proportion of patients with ICH growth at 48 h.

Ethical considerations:

An approval of the study was obtained from the Research Ethical Committee, Faculty of Medicine Menoufia University. The study was registered with 5/2020ANET8. Written informed consents were obtained from legally acceptable representative of comatose participants after explanation of benefits and risks. Privacy of all patients' data was granted. There was a code number for every patient file that includes all investigations.

Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. Qualitative data were expressed as number and percentage. Quantitative data were expressed as mean, standard deviation, and median (minimum and maximum). Data were tested for normality using Kolmogorov-Smirnov test. All tests were 2 tailed. The unpaired t-test was used to compare the means of the two groups. Chi-square (χ^2) test or Fisher's exact test (FET) was used for comparison between groups as regards qualitative data. A significant p-value was considered when it is equal or less than 0.05.

RESULTS

Patients in both groups were matched for age, gender, and BMI with no statistically significant differences in the previous medical history or the modes of trauma in both groups (Table 1).

Table (1): Demographic data in the studied groups

			TXA group n = 20	Placebo group n = 20	Test value	P-value	Sig.
Age	**Mean ± SD**		35.90 ± 12.307	33.90 ±13.848	0.483*	0.632	NS
	Range		18- 60	19 – 65			
Gender	**Male**	**N**	13	15	0.476§	0.731	NS
		%	65.0%	75.0%			
	Female	**N**	7	5			
		%	35.0%	25.0%			
BMI	**Mean± SD**		22.60 ± 2.06	21.50 ± 1.395	1.98*	0.055	NS
	Range		18- 25	19- 24			
Previous medical history	**Free**	**N**	10	13	9.01§	0.341	NS
		%	50%	65%			
	Hypertension	**N**	7	4			
		%	35%	20%			
	DM	**N**	4	2			
		%	20%	10%			
	Epilepsy	**N**	1	0			
		%	5%	0%			
	Ischemic heart disease	**N**	1	0			
		%	5%	0%			
	Viral hepatitis	**N**	0	4			
		%	0%	20%			
Mode of trauma	**Road traffic accident**	**N**	*14*	*15*	1.03§	0.596	NS
		%	*70.0%*	*75.0%*			
	Falling from height	**N**	*5*	*5*			
		%	*25.0%*	*25.0%*			
	Localized trauma to head	**N**	*1*	*0*			
		%	*5.0%*	*0.0%*			

SD= standard deviation, -comparison between groups done by *Student T test, §Pearson Chi-Square test

There was no statistically significant difference between the study groups regarding the type of ICH in brain CT of admission (intracerebral hemorrhage (p=1.00), subdural hemorrhage (p=0.501), epidural hemorrhage (p=1.00) and subarachnoid hemorrhage (p= 0.168) as shown in table (2).

Table (2): Type of ICH on admission in the studied groups

		TXA group n = 20	Placebo group n = 20	Test value	P-value	Sig.
Intracerebral hemorrhage	**n**	10/20	9/20	FET	1.00*	NS
	%	50.0%	45.0%			
Subdural hemorrhage	**n**	5/20	8/20	FET	0.501	NS
	%	25.0%	40.0%			
Epidural hemorrhage	**n**	3/20	3/20	0.0§	1.00	NS
	%	15.0%	15.0%			
Subarachnoid hemorrhage	**n**	8/20	4/20	1.91§	0.168	NS
	%	40.0%	20.0%			

Comparison between groups done by *FET=Fischer- Exact test, §Pearson Chi-Square test

There was statistical significant reduction in the volume of ICH after 48 hours (p= 0.021) in TXA group compared to placebo group. However, there was no statistical significant difference between the study groups regarding volume of ICH on admission (p= 0.503) and after 24 hours (p= 0.117).

In TXA group, there was high statistically significant reduction in volume of ICH after 48 hours only compared to on admission. While, in placebo group, there was statistically significant increase in volume of ICH after 24 and 48 hours compared to on admission (Table 3)

Table (3): Volume of ICH in the studied groups

		TXA group	Placebo group	Test value	P-value	Sig.
		n = 20	n = 20			
volume of ICH on admission	Mean	12.10	13.85	0.677	0.503*	NS
	SD	7.96	8.39			
	Median	10.00	13.50			
volume of ICH after 24 h	Mean	11.05	15.20	1.6	0.117	NS
	SD	7.62	8.72			
	Median	10.00	16.00			
Test value		1.2	15.02			
P-value		2.02	0.027			
Sig		NS	S			
volume of ICH after 48h	Mean	9.15	15.35	2.42§	**0.021**	**S**
	SD	7.29	8.87			
	Median	9.50	16.00			
Test value		44.04	61.0			
P-value		**<0.001**	**<0.001**			
Sig.		**HS**	**HS**			

-Comparison between groups done by independent samples Student T test, comparison inside the same group done by One Way ANOVA of repeated measures.

The incidence of brain edema, hydrocephalus and infarction were significantly lower in TXA group compared to placebo group after 24 and 48 hours (Table 4).

Table (4): CT findings after 24 hours and 48 hours in the studied groups

			TXA group	Placebo group	Test value	P-value	Sig.
			n = 20	n = 20			
CT findings after 24 hours	Brain edema	n	7	15	-	0.025*	S
		%	35.0%	75.0%			
	Hydrocephalus	n	4	12	6,67§	0.022	S
		%	20.0%	60.0%			
	Infarction	n	2	1	8,01§	0,005	HS
		%	10.0%	5.0%			
CT findings after 48 hours	Brain edema	n	4	12	-	0.022*	S
		%	20.0%	60.0%			
	Hydrocephalus	n	3	10	-	0.018	S
		%	15.0%	50.0%			
	Infarction	n	3	4	*5.59§*	*0.027*	S
		%	15.0%	20.0%			

-Comparison between groups done by *FET= Fischer- Exact test, §Pearson Chi-Square

There was no statistically significant difference between the study groups regarding GCS on admission (p= 0.619), after 24 hours (p= 0.435) or after 48 hours (p= 0.176). In TXA group, there was highly statistically significant improvement in GCS after 48 hours only compared to GCS on admission. While in placebo group, there was no statistically significant difference in GCS after 24 or 48 hrs compared to on admission (Table 5).

Table (5): GCS changes in the studied groups

		TXA group	Placebo group	Test value	P-value	Sig.
		n = 20	n = 20			
GCS on admission	**Mean**	7.25	7.65	0.501	0.619	NS
	SD	2.34	2.70			
	Median	7.00	7.00			
GCS after 24 hours	**Mean**	9.50	8.55	0.788	0.435	NS
	SD	3.79	3.83			
	Median	11.00	8.50			
GCS after 48 hours	**Mean**	10.50	8.65	1.38§	0.176	NS
	SD	4.47	4.00			
	Median	12.50	9.00			
Test value		17.32	1.863			
P-value		**0.001**	0.188			
Sig.		**HS**	NS			

-Comparison between groups done by independent samples Student T test

There was no statistically significant difference between the study groups regarding D dimer, fibrinogen, and INR during 48 hrs as shown in table (6).

Table (6): Laboratory investigations done for the studied groups

		TXA group	Placebo group	Test value	P-value	Sig.
		n = 20	n = 20			
D dimer on admission	**Mean**	*281.80*	*243.75*	0.203	.839	NS
	SD	*216.22*	*120.79*			
	Median	*200.00*	*215.00*			
D dimer after 48 hours	**Mean**	*394.00*	*363.40*	0.027	.978	NS
	SD	*271.42*	*224.15*			
	Median	*325.00*	*300.00*			
Fibrinogen level on admission	**Mean**	*264.35*	*290.35*	0.880	.379	NS
	SD	*70.97*	*100.02*			
	Median	*260.00*	*299.00*			
Fibrinogen level after 48 hours	**Mean**	*348.40*	*393.70*	0.758	.448	NS
	SD	*143.58*	*172.21*			
	Median	*330.00*	*330.00*			
INR on admission	**Mean**	*1.26*	*1.23*	1.354	.176	NS
	SD	*.16*	*.31*			
	Median	*1.20*	*1.10*			
INR after 48 hours	**Mean**	*1.42*	*1.42*	0.041	.967	NS
	SD	*.26*	*.28*			
	Median	*1.40*	*1.35*			

- Comparison between groups done by independent samples Student T test

There was statistical significant reduction in need of surgical intervention (p= 0.05) and blood transfusion in TXA group (p= 0.04) compared to placebo group (Table 7).

Table (7): Need for surgical intervention and blood transfusion in the studied groups during 48 hrs

		TXA group	Placebo group	Test value	P-value	Sig.
		n = 20	n = 20			
Need Surgical intervention	**N**	4	7	26.7	0.05	S
	%	20.0%	35.0%			
Need of blood transfusion	**N**	*2*	6	57.8	0.04 *	S
	%	10.0%	30.0%			

-comparison between groups done by *Fischer- Exact test, §Pearson Chi-Square test

There was statistically significant reduction in the incidence of hydrocephalus in TXA than in placebo group (p= 0.018) through the in-hospital follow up (for 28 days). While, there was no statistically significant difference between the study groups regarding the incidence of infarction (p= 0.465) and DVT and pulmonary embolism (p= 1.00) as shown in table (8).

Table (8): In-hospital complications recorded among the studied groups within 28 days

			TXA group	Placebo group	Test value	P-value	Sig.
			n = 20	n = 20			
Complications	**Infarction**	**n**	4	6	0.533	0.465	NS
		%	20.0%	30.0%			
	Hydrocephalus	**n**	3	10	5.58	**0.018**	S
		%	15.0%	50.0%			
	DVT and pulmonary embolism	**n**	1	0	1.03	1.00	NS
		%	5.0%	0.0%			

-comparison between groups done by Pearson Chi-Square test

DISCUSSION

Our study revealed that there was significant increase of ICH through the first 48 hrs after TBI in control group. While, using of TXA resulted in significant reduction in the volume of ICH after 48 hours of admission, decreasing the need of blood transfusion, surgical intervention, and the incidence of complications. Moreover, there was no effect on coagulation profile. This is explained by that TXA is an antifibrinolytic drug that inhibits plasmin formation and displaces plasminogen from the fibrin surface. It inhibits plasmin and partially inhibits fibrinogenolysis at higher concentrations. Tranexamic acid is also thought to exert an anti-inflammatory effect (by inhibiting plasmin mediated activation of complement, monocytes, and neutrophils) and may improve platelet function in certain circumstances [(6)].

Our study revealed that the volume of ICH in TXA group on admission ranged from 2-30 ml, after 24 hours ranged from 0-25 ml, and after 48 hours ranged from 0-20 ml. While, the volume of ICH in placebo group on admission ranged from 2-35 ml, after 24hrs ranged from 2-35 ml and after 48 hours ranged from 3-35 ml.

There was statistically significant reduction in the volume of ICH after 48 hours in TXA group than in placebo group. Although, there was no statistically significant difference between the study groups regarding the volume of ICH on admission or after 24 hours, there was statistically significant increase in the volume of ICH in placebo group after 24 and 48 hours than on admission. This is in agreement with **Perel *et al.*** [(7)] where they studied 270 patients, 133 allocated to TXA and 137 allocated to placebo. The mean total hemorrhage growth was 5.9 ml and 8.1 ml in the TXA and placebo group respectively. The adjusted analysis showed a greater reduction in total hemorrhage growth in the TXA group than in the placebo group. Also, in study by **Weng *et al.*** [(8)] they found statistically significant reduction of volume of ICH in TXA group. While, in **Jokar et *al.*** [(9)] although brain CT scan showed a significant increase in hemorrhage volume in both groups after 48 hours, it was significantly lesser in TXA group than in the control group. The mean total hemorrhage expansion was 1.7 ± 9.7 ml and 4.3 ± 12.9 ml in TXA and control groups respectively ($p < 0.001$) and that was in agreement with our study. In addition, **Fakharian *et al.*** [(10)] agree

with our results as they found that there was no significant reduction in the growth of hemorrhagic lesion after 24 hours in the TXA than in placebo group (9.4 ± 15.3 and 10.2 ± 10.1 respectively), but they included some patients, which had new hemorrhage that not appeared in first CT, that was not included in our study.

On the other hand, **Yutthakasemsunt *et al.* [11]**, studied 120 patients received TXA and 118 patients were placebo. Although, they noticed that progressive ICH was present in 21 (18%) in TXA and in 32 (27%) in placebo group, they reported that this difference was not statistically significant, which also disagree with our study. This might be because progressive intracerebral hemorrhage (PIH) was defined as an intracranial hemorrhage seen on the second CT scan that was not seen on the first CT scan, or an intracranial hemorrhage seen on the first scan that had expanded by 25% or more on any dimension (height, length, or width) on the second scan. But, in our study we considered any increase in volume of ICH. As well as patients with no hemorrhage in the first CT brain were not included in our study.

In our study, although there was no significant difference between the two groups in the GCS allover 48 hours, there was significant improvement in GCS in TXA group after 48 hours than on admission. **Fakharian *et al.* [10]**, support our results as they found no statistically significant difference in GCS between the two groups. Also, **Weng *et al.* [8]** revealed significant improvement in GCS in patients received tranexamic acid after 48 hours than at time of arrival, which is in agreement with our findings.

In our study, tranexamic acid significantly reduced the surgical intervention and the need of blood transfusion. Where, only 4 (20%) patients in TXA group needed surgical intervention and 2 (10%) patients of them needed blood transfusion. While, in placebo group, 7 (35%) patients needed surgical intervention and 6 (30%) patients needed blood transfusion. **Walha *et al.* [12]** disagree with our study as in control group there were 16 (19%) patients of 84 needed surgical interventions, and in TXA group 23 (24%) patients of 96 needed surgical interventions. Also, **Yutthakasemsunt *et al.* [11]** reported that in TXA group, 3 patients needed surgical intervention out of 120 (3%) and in placebo group no patients needed surgical intervention. Also, in **Binz *et al.* [13]** study, requirement for surgery and need for blood transfusion were equivalent between the two groups.

The incidence of in-hospital complications recorded for 28 days (cerebral infarction, hydrocephalus, pulmonary embolism (PEs), and deep vein thromboses (DVT) in placebo group were significantly more than that in TXA group. **Yutthakasemsunt *et al.* [11]** showed that no patient in the TXA treated group developed any vascular occlusive event, whereas 3 patients developed a new stroke in the placebo group, which is in agreement with our study. However, In **Binz *et al.* [13]** there were no significant differences between the two groups in the occurrence of vascular occlusive events (myocardial infarctions, strokes, PEs, and DVT, and this disagrees with our study. While, **Walha *et al.* [12]** demonstrated that TXA led to a greater rate of pulmonary embolism, and they used same doses and technique**.**

Fakharian *et al.* [10] and **Walha *et al.* [12]** support our study as there was no statistically significant difference between the studied groups regarding D-dimer, fibrinogen, and INR on admission or after 48 hrs.

Early administration of tranexamic acid (within 8 hours of injury onset) can limit the extent of bleeding before the hemorrhagic volume may become dangerous, while late administration can be useless. Early administration of tranexamic acid is associated with less hospital resources usage, lower mortality rate and better functional outcome. New studies as **Jokar *et al.* [9]** and **Atia *et al.* [14]** approved earlier administration of tranexamic acid (within 3 hours of injury onset) may be more useful in limiting extent of bleeding.

CONCLUSION

TBI that is associated with intracranial hemorrhage has high risk of coagulopathy, which may worsen hemorrhagic mass volume. Administration of tranexamic acid can limit the extent of bleeding and its side effects without evidence of increased risk of thromboembolic events. Early administration of tranexamic acid is associated with less hospital resources usage, lower mortality rate and better functional outcome

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