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Research Article
Effectiveness and Safety of Early Tranexamic Acid in Patients with Acute Traumatic Brain Injuries

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Abstract

Background and Objective: Tranexamic acid prevents bleeding by fibrinolysis. In patients with acute traumatic injuries, tranexamic acid is widely used in hospitals but it is not clear whether early tranexamic acid is beneficial for patients with acute traumatic brain injuries. The objectives of the study were to evaluate the effectiveness and safety of early tranexamic acid in patients with acute traumatic brain injuries regarding morbidity and mortality. **Materials and Methods:** Patients with acute traumatic brain injuries have received tranexamic acid within 3 hrs of injuries (TX cohort, n = 149) or have not received it (NS cohort, n = 115) because pregnant women, had unknown onset time for trauma, need for reconstructive surgeries, had cerebral oedema and/or subarachnoid haemorrhage. **Results:** The number of deaths within 24 hrs of injuries was fewer among patients who received tranexamic acid than those who did not receive tranexamic acid (7 vs. 10%). Reduction in the risk of death in patients with mild to moderate head injuries (Glasgow Coma Scale score: 9-12) on the administration of tranexamic acid ($p = 0.042$). Administration of tranexamic acid has reduced the risk of death in patients with less severely injured patients (two reacted pupils) ($p = 0.008$). Tranexamic acid had no adverse effects. **Conclusion:** Tranexamic acid treatment initiated within 3 hrs of injuries is effective in acute traumatic brain injuries especially in cases of mild to moderate head injuries.

Key words: Acute traumatic brain injury, Glasgow coma scale score, intracranial bleeding, tranexamic acid, morbidity, mortality, reconstructive surgeries

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Traumatic brain injuries in China are a major health concern because there are more in China than the other countries[1]. Road traffic incidents are the most common cause of traumatic brain injuries in China[2]. In traumatic brain injuries, intracranial bleeding is the most common complication and has the risk of disability and death[3]. Mainly bleeding is starting from the moment of impact, it can continue for several hours after that[4]. Ongoing intracranial bleeding can increase the risk of higher intracranial pressure, brain herniation and death[3].

Tranexamic acid prevents bleeding by fibrinolysis (inhibiting the enzymatic breakdown of fibrin blood clots)[4]. The CRASH-2 trial[5,6], the CRASH-3 trial[4], a randomized trial[7] and a meta-analysis[8] show that tranexamic acid reduces the death of an individual with traumatic brain injuries in cases of major extra cranial bleeding. However, the chances of survival are only if it is administered with 3 hrs of injuries[9]. However, randomized trials[10,11] and the BRAIN-PROTECT trial[3] are reported that tranexamic acid does not reduce the death of individuals with traumatic brain injuries. In patients with acute traumatic injuries, tranexamic acid is widely used in hospitals but it is not clear whether early tranexamic acid is beneficial for patients with acute traumatic brain injuries.

The objectives of the retrospective analysis were to evaluate the effectiveness and safety of early tranexamic acid in patients with acute traumatic brain injuries regarding morbidity and mortality.

MATERIALS AND METHODS

Study area: The study was carried out at the Department of Emergency of the First Affiliated Hospital of Soochow University, China from 15 June, 2019-12 March, 2021.

Ethics approval and consent to participate: The designed protocol (TXA21TBI_20 dated 30 May, 2020) was approved by the First Affiliated Hospital of Soochow University review board and the Chinese Society of Traumatology. The reporting of the study adheres to the Chinese law and the latest version (V2008) of the Declarations of Helsinki. The relatives of patients have signed an informed consent form regarding treatment intervention(s) and publication of the study including anonymized information of patients in the form of an article(s) during hospitalization.

Inclusion criteria: Patients 18 years and above with traumatic brain injuries and admitted to the emergency department of the hospital within 3 hrs of injuries, had a 12 or fewer Glasgow Coma Scale score or had reported intracranial bleeding in the computed tomography scan were included in the analysis.

Exclusion criteria: Patients whose complete data not available at the hospital records of patients were excluded from analysis.

Cohort: A total of 149 patients with acute traumatic brain injuries have received 1 g tranexamic acid (Nanjing Hailing Pharmaceutical Co., Ltd, China) over 10 min in 100 mL of normal saline (Shanghai Baxter Healthcare Co., Ltd, China) then infusion of 1 g of tranexamic acid in 500 mL normal saline over 8 hrs (TX cohort) within 3 hrs of injuries. A total of 115 patients have received normal saline only (NS cohort) because pregnant women, had unknown onset time for trauma, need for reconstructive surgeries, had cerebral oedema and/or subarachnoid hemorrhage[7].

Sample size calculation: The study was assumed that there would be a maximum of 20% of mortality after acute traumatic head injuries[12]. The sample size (minimum patients required in each cohort) was calculated based on assumed mortality, 5% Type-I error and 10% Type-II error and was reported to be 100.

Severity of injury: If the Glasgow Coma Scale score was 9-12, then it was considered as mild to moderate injuries. If the Glasgow Coma Scale score was 3-8, then it was considered as severe injuries[4].

Death: Data regarding head injuries-related and/or other reasons related to death were collected and analyzed.

Early death: Data regarding head injuries-related death and/or other reasons related to death within 24 hrs of admission to the hospitals were collected and analyzed.

Data regarding morbidities, intensive care unit(s) stay, treatment-emergent adverse effects and other adverse events were collected and analyzed.

Statistical analysis: SPSS 26.0, IBM Corporation, Armonk, NY, USA was used for statistical analysis purposes. The Fischer exact test or Chi-square test for Independence for categorical data and unpaired t-test for continuous data were performed for statistical analysis. Univariate following multivariate analysis was used to evaluate the effects of demographical and clinical conditions of patients on morbidity of patients.

Results were considered significant if a p-value less than 0.05 at 95% of confidence level with odd ratio.

RESULTS

Study population: From 15 June, 2019-12 March, 2021, a total of 281 patients with acute traumatic brain injuries were admitted to the department of emergency of the First Affiliated Hospital of Soochow University, China and the referring hospital within 3 hrs of injuries. Among them, the complete data of 17 patients were not available in the patients' records of hospitals. Therefore, data of these patients (n = 17) were excluded from the analysis. Data regarding demographical and clinical conditions of patients, morbidity and mortality of a total of 264 patients were included in the analysis. The flow diagram of the study is presented in Fig. 1.

Demographical and clinical characters: There were no significant differences between those who received tranexamic acid and those have not received it for the demographical and clinical characters of patients at the time of hospital admission (Table 1).

Death: A total of 27 patients from the TX cohort and 22 patients from the NS cohort have died (p = 0.874). There were no significant differences between those who received tranexamic acid and those have not received it for death and time of death after injuries (Table 2).

Risk factor associated with death: Univariate analysis was confirmed that onset time of acute traumatic injuries 2.9-3 hrs, systolic blood pressure 140 mmHg or more, severe traumatic brain injuries (Glasgow Coma Scale score: 3-8), age 60 years or more and none reacted pupil was associated with the death of the patient. The details of univariate analysis for the evaluation of the risk factor associated with death among patients who received Tranexamic acid is reported in Table 3. The multivariate analysis reported that there was a reduction in the risk of death in patients with mild to moderate head injuries (Glasgow Coma Scale score: 9-12) on the administration of tranexamic acid (p = 0.042, odd ratio: 1.141, 95% confidence interval: 0.612-0.971). However, severe traumatic brain injuries (Glasgow Coma Scale score: 3-8) were an independent parameter associated with death. Also, administration of tranexamic acid had reduced the risk of death in patients with less severely injured patients (two reacted pupils) (p = 0.008, odd ratio: 1.153, 95% confidence interval: 0.592-0.983). The details of multivariate analysis for the evaluation of the risk factor associated with death among patients who received Tranexamic acid is reported in Table 4.

Table 1: Demographical and clinical characters of patients at the time of hospital admission

		Characteristics		
		Cohorts		
Treatments		TX Tranexamic acid	NS Normal saline	Comparisons
Numbers of patients		149	115	p-value
Sex	Men	106 (71)	81 (70)	0.998
	Women	43 (29)	34 (30)	
Age (years)	≤30	39 (26)	31 (27)	0.927
	31-60	67 (45)	49 (43)	
	>61	43 (29)	35 (30)	
Time of acute traumatic injuries (hrs)	≤1	28 (19)	21 (18)	0.869
	2 to 2.9	44 (30)	31 (27)	
	2.9-3	77 (51)	63 (55)	
Systolic blood pressure (mm Hg)	≤89	7 (5)	3 (3)	0.778
	90-119	45 (30)	32 (28)	
	120-139	51 (34)	41 (36)	
	≥140	46 (31)	39 (33)	
Severity of injury	Severe (Glasgow coma scale score: 3-8)	62 (42)	47 (41)	0.997
	Mild to moderate (Glasgow coma scale score: 9-12)	87 (58)	68 (59)	
Pupil reaction	None reacted	17 (11)	12 (10)	0.916
	One reacted	24 (16)	17 (15)	
	Two reacted	108 (73)	86 (75)	
Intensive care unit(s) stay (hrs)		81±12	83±9	0.137

Categorical variables are demonstrated as frequency (percentages) and continuous variables are demonstrated as Mean±Standard deviation (SD), Fischer exact test or Chi-square test for Independence for categorical variables and unpaired t-test for continuous variables were used for statistical analysis. A p<0.05 was considered significant

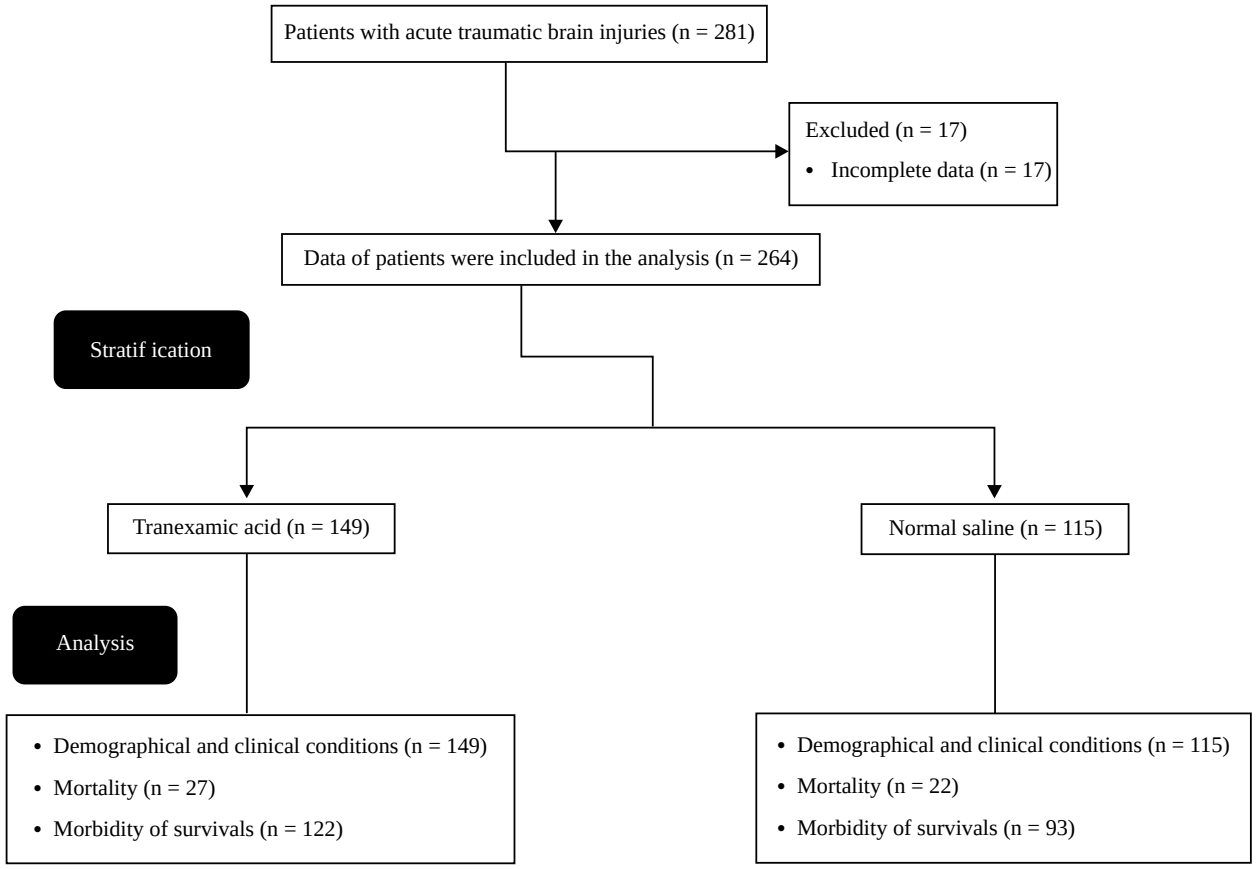

Fig. 1: Flow diagram of the study

Table 2: Death of patients after admission of hospital admission for treatment

	Parameters		
	Cohorts		
	TX	NS	
Treatments	Tranexamic acid	Normal saline	Comparisons
Numbers of patients	149	115	p-value
Death	27 (18)	22 (19)	0.874
Early death	10 (7)	11 (10)	0.493
Time of death after injuries (h)	62±8	60±9	0.058

Categorical variables are demonstrated as frequency (percentages) and continuous variables are demonstrated as Mean±Standard deviation (SD), Fischer exact test or Chi-square test for Independence for categorical variables and unpaired t-test for continuous variables were used for statistical analysis, A $p<0.05$ was considered significant

Table 3: Univariate analysis for the evaluation of the risk factor associated with death among patients who received Tranexamic acid

	Numbers of patients died (27)		
Characteristics	Odd ration	Confidence interval (95%)	p-value
Sex (women vs. men)	0.785	0.524-0.625	0.067
Age (>61 years* vs. ≤60 years)	1.008	0.452-0.852	0.045
Time of acute traumatic injuries (2.9-3 hrs* vs. ≤2.89)	1.142	0.351-0.671	0.041
Systolic blood pressure (≥140 mmHg* vs. ≤139 mmHg)	1.158	0.456-0.987	0.042
The severity of injury (Severe (Glasgow coma scale score: 3-8) *vs. Mild to moderate (Glasgow coma scale score: 9-12)	4.521	0.112-2.151	0.011
Pupil reaction (None reacted* vs. at least one reacted)	5.312	0.253-2.453	0.002
Intensive care unit(s) stay (50 hrs vs ≤49 hrs)	0.852	0.453-0.659	0.105

A value $p<0.05$ and odd ratio >1 considered significant, *Significant value

Table 4: Multivariate analysis for the evaluation of the risk factor associated with death among patients who received Tranexamic acid

	Numbers of patients died (27)		
Characteristics	Odd ration	Confidence interval (95%)	p-value
Age (>61 years vs. ≤60 years)	0.918	0. 521-0.763	0.081
Time of acute traumatic injuries (2.9-3 hrs vs. ≤2.89)	0.952	0.452-0.615	0.053
Systolic blood pressure (≥140 mmHg vs. ≤139 mmHg)	0.892	0.462-0.871	0.062
The severity of injury (Severe (Glasgow coma scale score: 3-8)* vs. Mild to moderate (Glasgow coma scale score: 9-12)	1.141	0.612-0.971	0.042
Pupil reaction (None reacted* vs. at least one reacted)	1.153	0.592-0.983	0.008

A value p<0.05 and odd ratio >1 considered significant, *Significant value

Table 5: Treatment-emergent adverse effects

	Cohorts		
Events	TX	NS	Comparisons
Treatments	Tranexamic acid	Normal saline	p-value
Survived patients	122	93	0.874
All vascular occlusive events	3 (2)	2 (2)	0.998
Pulmonary embolism	2 (2)	1 (1)	0.997
Deep vein thrombosis	2 (2)	1 (1)	0.997
Stroke	2 (2)	1 (1)	0.997
Myocardial infarction	3 (2)	1 (1)	0.635
Renal failure	4 (3)	2 (2)	0.701
Sepsis	10 (8)	6 (6)	0.795
Seizure	5 (4)	2 (2)	0.702
Gastrointestinal bleeding	2 (2)	1 (1)	0.997

Variables are demonstrated as frequency (percentages), Fischer exact test was used for statistical analysis, A p<0.05 was considered significant

Table 6: Other adverse events

	Cohorts		
Events	TX	NS	Comparisons
Treatments	Tranexamic acid	Normal saline	p-value
Survived patients	122	93	0.874
Pneumonia	7 (6)	4 (4)	0.761
Urinary tract infection	8 (7)	3 (3)	0.357
Allergic reaction	5 (4)	5 (5)	0.749
Rectal bleeding	1 (1)	1 (1)	0.998
Pulmonary oedema	1 (1)	0 (0)	0.997
Painful urination	7 (6)	5 (5)	0.996
Respiratory infection	3 (2)	3 (3)	0.995
Wound infection	8 (7)	5 (5)	0.781

Variables are demonstrated as frequency (percentages), Fischer exact test was used for statistical analysis, A p<0.05 was considered significant

Treatment-emergent adverse effects and other adverse events: A total of 122 patients from the TX cohort and 93 patients from the NS cohort were survived. Administration of tranexamic acid was not responsible for any kind of treatment-emergent adverse effects (p>0.05 for all, Table 5) and the other adverse events (p>0.05 for all, Table 6) among survivals.

DISCUSSION

The study reported that administration of tranexamic acid was reduced the risk of death in cases of mild to moderate head injuries without any adverse events if it was administered within 3 hrs of injuries. The results of outcome measures of the current study were consistent with those of the CRASH-2 trial[5,6], the CRASH-3 trial[4] and a meta-analysis[8] but not consistent with those of randomized trials[10,11] and the BRAIN-PROTECT trial[3]. The reason for contradictory results of outcome measures of the current study with those of a randomized trial[10] is that a randomized trial[10] is administered tranexamic acid within 8 hrs of traumatic injuries. While the current study was administered tranexamic acid within 3 hrs of traumatic brain injuries. Survival benefits are evident only in patients whose treatment is initiated within 3 hrs of injury[13]. The reason for the contradictory results of outcome measures of the current study with those of the BRAIN-PROTECT trial[3] is that the BRAIN-PROTECT trial[3] has administered tranexamic acid in more severely injured patients only. The reason for the contradictory results of outcome measures of the current study with those of a randomized trial[11] is that a randomized

trial[11] has not independently examined patients with mild to moderate and severe traumatic head injuries. The effect of tranexamic acid is dependent on the severity of injuries[4]. Tranexamic acid treatment initiated within 3 hrs of injuries is effective in acute traumatic brain injuries especially in cases of mild to moderate head injuries.

The study reported that severe traumatic brain injuries were an independent parameter associated with death. The results of the risk factor associated with the death of the current study were consistent with those of the CRASH-3 trial[4] and a randomized trial[10]. Patients with severe traumatic brain injuries had extensive intracranial haemorrhage before administration of tranexamic acid[4]. Patients with severe head injury have received fewer benefits from tranexamic acid than those with mild to moderate head injury.

The number of early deaths (within 24 hrs of injuries) was fewer among patients who received tranexamic acid than those who did not receive tranexamic acid (7 vs. 10%). The results of early deaths of the current study were consistent with those of the CRASH-2 trial[5,6,13], the CRASH-3 trial[4], a randomized trial[11] and a meta-analysis[9]. Early death is due to bleeding[4]. Tranexamic acid treatment within 3 hrs of injuries is effective to reduce the early death of patients because tranexamic acid has the greatest effect on the day of injuries. The number of deaths was statistically insignificant between patients who received tranexamic acid and those who did not receive tranexamic acid. The results of the deaths of the current study were consistent with those of the CRASH-2 trial[5,6], the CRASH-3 trial[4] and the randomized trial[10,11]. Tranexamic acid has the greatest effect on the day of administration than after the effect of tranexamic acid is attenuated because patients were victims of non-bleeding-related pathophysiology[4]. Tranexamic acid treatment within 3 hrs of injuries is moderately effective to reduce the death of patients. Also, calculation of onset time of injuries is difficult because the call of emergency help and arrival to the hospital was considered as onset time of injuries.

In the limitations of the study, for example, retrospective analysis and lack of randomized trial. A randomized trial is not possible in the emergency department because the emergency staff has to educate regarding emergency conditions. Death was not differentiated into head-related death and non-head-related death. The decision of the administration of tranexamic acid to patients with traumatic brain injuries was not based on the progression of intracranial haemorrhage. However, the current study was reported that less severely injured patients (two reacted pupils) had benefited from the administration of tranexamic acid.

CONCLUSION

Tranexamic acid treatment initiated within 3 hrs of injuries is effective in acute traumatic brain injuries especially in cases of mild to moderate head injuries. Tranexamic acid has the greatest effect on the day of injuries. Tranexamic acid treatment within 3 hrs of injuries is moderately effective to reduce the death of patients.

SIGNIFICANCE STATEMENT

Morbidity and mortality analysis for patients with acute traumatic brain injuries reported that Tranexamic acid treatment initiated within 3 hrs of injuries is effective in acute traumatic brain injuries especially in cases of mild to moderate head injuries. The finding will help emergency physicians to uncover the critical issue regarding traumatic brain injuries.

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