ORIGINAL ARTICLE

Tranexamic acid in traumatic brain injury

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ABSTRACT

Background: Some surgeons advocate the usage of tranexamic acid (TXA) in traumatic brain injury (TBI). The aim of this study is to determine the effectiveness and safety of TXA in improving the outcome of TBI patients and in reducing the rate of clot expansion and mortality in TBI as compared to those without TXA.

Methods: This is a prospective observational cohort study conducted in Sarawak General Hospital, Malaysia. Patients 12 years of age and older with mild to severe TBI who had a brain computed tomography (CT) done within eight hours of injury were enrolled in the study. A total of 334 patients were recruited from the 5th of August 2016 until the 8th of March 2018 in Sarawak General Hospital. In all 167 of them were administered with TXA and another 167 of the patients were not. The primary outcome expected is the number of good outcomes in isolated TBI patients given TXA. Good outcome is defined by Glasgow Outcome Score-Extended (GOSE) of five and above. Secondary outcome was clot expansion of an intracranial bleed seen on the first scan that had expanded by 25% or more on any dimension on the second scan.

Results: The TXA did not show significant trend of good outcome in terms of GOSE (p=0.763). However, for moderate and severe acute subdural haemorrhage (SDH) subgroups, there was a significant difference (p=0.042). Clot expansion was present in 14 patients (12.7%) with TXA given and in 54 patients (38.8%) without TXA. The difference was statistically significant (p<0.001). Of the patients who received TXA, there was one case (0.6%) of deep vein thrombosis. Apart from that, TXA showed non-significant trend in reducing mortality (p=0.474).

Conclusions: Tranexamic acid reduces the rate of clot expansion in TBI by 26.1% (38.8-12.7%) without significantly increasing the risk of a thrombotic event. It can also improve the outcome of moderate and severe TBI patients with acute SDH.

KEYWORDS:
Traumatic brain injury, tranexamic acid, outcome, clot expansion

INTRODUCTION

Traumatic brain injury (TBI) is a complex condition that will stay as a major concern for the public in years to come. Worldwide, it is the greatest contributor to disability and death among all trauma-related injuries.[1] Annually, about 69 million people will sustain some form of TBI, of which 8% of them will be severe, 11% moderate and 81% mild in severity.[2] TBI is also known as the 'silent epidemic' because problems that arose from TBI are usually not immediately noticeable.[3,4] The real incidence is always underestimated, and the society is usually unaware of the long-term impact of TBI.[5] Furthermore, the reports of the incidences of TBI in underdeveloped and developing countries are scarce. A large survey-based study in these countries showed that a lifetime prevalence of TBI from <1% in China to nearly 15% in Mexico and Venezuela.[6] Road traffic accidents (RTA) are the major contributor of TBI.[7-9] In Malaysia, there is no published data on the incidence of TBI. Hence, this is also one of the reasons for which this study was carried out albeit in a single city in Malaysia. TBI is associated with intracranial bleed in 25 to 45%, 3 to 12% and 0.2% of severe, moderate and mild TBI patients respectively.[10] Bleeding can still occur after the initial brain scan and might lead to further deterioration of the patient.[11] Coagulopathy affects about one-third of patients with TBI and increased fibrinolysis is a common feature of coagulopathy.[12,13] During elective surgery, the usage of an antifibrinolytic agent like tranexamic acid (TXA) is effective in reducing bleeding and mortality with no increased side effects.[14,15] In polytrauma, TXA was proven to be effective in reducing mortality.[11] TXA is an inhibitor of fibrinolysis that functions by inhibiting plasminogen activation. Injury to blood vessel endothelium results in the release of tissue factors and exposed collagen which in turn lead to the activation of the extrinsic and intrinsic coagulation cascade. Thrombin formation then occurs leading to the creation of clot with the help of platelet. Subsequently, plasminogen will bind to the clot and is converted to plasmin that will cleave the fibrin clots into fibrin degradation products, allowing clots to dissolve.[16] Hence, by inhibiting the conversion of plasminogen to plasmin using TXA, the fibrin clot will remain undisturbed (Figure 1). However, the usage of TXA in isolated TBI is still debatable. Some surgeons advocate the usage of TXA in TBI, but some do not due to its thrombotic properties. However, a Cochrane review reported that TXA does not significantly increase the risk of myocardial infarction, stroke, deep vein thrombosis and pulmonary embolism.[17] Thus far, there are only two randomised controlled trials touching on tranexamic acid and clot expansion in isolated traumatic brain injury. In a Thai study, it was noted that clot expansion in TBI was present in 18% of patients with TXA given and in 32% of patients without TXA. However, the difference was not significant.[18] Meanwhile, in an Iranian

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study, it showed significantly less clot expansion in patients that were given TXA (p=0.04).[19]

The general aim of this study was to determine the prevalence of good outcome in isolated TBI patients given TXA and the specific aims are to evaluate the effectiveness of tranexamic acid as an anti-fibrinolytic agent in reducing the rate of clot expansion and mortality in TBI as compared to those without TXA.

METHODS

Study setting and period

The prospective observational cohort study was carried out at the neurosurgery department of Sarawak General Hospital, Kuching, Sarawak, Malaysia from August 2016 to March 2018. The trial protocol was approved by the Medical Research Ethics Committee (MREC) of Malaysia with an approval number of NMRR-16-1303-31861.

Sample size

The estimated prevalence of good outcome based on a pilot data (10 patients) was 40.0% and the estimated number of patients for this group was 300 per year in our centre. Based on the prevalence formula using a 95% confidence level with a population estimated at 300, this study needed a minimum of 165 patients with the drugs (TXA) given to be able to detect 40% prevalence of good outcome with worst acceptable range is within ±5%. The sample size calculation was conducted using Epi InfoTM version 7.2.0.1 software. As the study needed at least 165 subjects with TXA given and another 165 subjects without TXA, the total sample size required was 330.

Patient population

All patients admitted to the adult neurosurgery ward, aged 12 years and above with isolated mild to severe TBI who had computed tomography of the brain (CTB) done within 8 hours of injury with any intracranial bleeding in CT brain were recruited. Patients were excluded if they were of Glasgow coma scale (GCS) 3 with fixed and dilated pupils or post cardiopulmonary resuscitation (CPR), pregnant, with major extracranial haemorrhage, with evidences of coagulopathy, receiving medication that can affect haemostasis, with pre-existing renal, cardiac or liver impairment, with known allergy to TXA and with recent (within 1 year) thrombo-embolic diseases like stroke, myocardial infarction, deep vein thrombosis (DVT) or pulmonary embolism. An entry form was used to assess the eligibility and to collect baseline information from traumatic brain injury patients of both arms, one with tranexamic acid and the other without.

Drug administrations

In the tranexamic acid group, a loading dose of IV TXA 1g over 10 minutes was given after the first CTB revealed intracranial bleed followed by maintenance dose of IV infusion of TXA 1g over 8 hours that was given after the loading dose. The decision to administer the drug depended on the preference of the on-call surgeons. Some surgeons believed that TXA can improve the outcome of TBI patients, but some did not.

Study outcomes

The primary outcome was the prevalence of good outcome in isolated TBI patients given TXA. Good outcome was defined by extended Glasgow Outcome Score (GOSE) of five or more and was assessed upon discharge, prior to death or at day 30 of admission if the patient was still warded. Early GOS scores can predict long-term functional outcome in patients with TBI.[20] Significant clot expansion is defined as the expansion of an intracranial bleed seen on the first scan that has expanded by 25%[18] or more on any dimension on the second scan that is done within 24 hours of trauma. Clot volume (ml) was calculated using the ABC/2 equation where A is the maximum length (cm), B is the length perpendicular to A on the same head CT slice and C is the number of slices multiplied by the slice thickness.[21] Other outcomes include blood transfusion, neurosurgical operation, death from all causes and any adverse effect of TXA. An outcome form was filled for each patient recruited.

Statistical analysis

Data were explored, screened and cleaned using IBM Statistical Package for the Social Sciences (SPSS) Version 22.0. Numerical variables were presented using mean and standard deviation while the categorical variable was presented using frequency and percentage. Independent T, Chi-square and Fisher exact tests were used to analyze and compare the difference between the baseline characteristics and TXA and the outcomes (mortality, clot expansion and Extended Glasgow Outcome Scale).

RESULTS

In all a total number of 745 patients with TBI who were admitted, 334 patients were recruited in this study (Figure 2). Of these 167 of them were administered with TXA drug and 167 other patients were not (Table I). The mean age of patients was 42.47 and 38.67 years for those without TXA and given TXA respectively. The difference of the mean age between the two groups was insignificant (p=0.074). Majority were males, constituting 81.4% for patients without TXA and 89.8% for patients who received TXA. Mean (SD) GCS on admission who received TXA was 10.25 (3.09) and 11.50 (3.08) those without TXA. The difference of the mean GCS was significant (p<0.001). For patients who did not receive TXA, 50.9% of them had a mild traumatic brain injury, 28.1% were moderate and 21.0% were severe. While for patients who received TXA, the percentage for the patient who had mild, moderate and severe TBI were 30.5%, 38.9%, and 30.5% respectively. Most of the patients suffered from intraparenchymal haemorrhage (IPH) which included cerebral contusion (47.9% for patients without TXA and 45.5% for patients with TXA).

Among those who received TXA, there was one case (0.6%) who demonstrated the side effect of deep vein thrombosis and none occurred in the group without TXA. In all 37.7% of the patients who received TXA underwent operation. For those who did not receive the drug, only 19.25% of them underwent operation. There were more patients (27.5%) in the TXA group who received blood transfusion compared to patients who did not (16.8%).

Table I: Baseline characteristics and outcomes of the participants

	Without TXA (n=167)		With TXA (n=167)		
	Mean (SD)	Frequency (%)	Mean (SD)	Frequency (%)	p value
Age	42.47 (21.35)		38.67 (18.88)		0.074[a]
Gender					
Male		136 (81.4)		150 (89.8)	0.042[b]
Female		31 (18.6)		17 (10.2)	
GCS on admission	11.50 (3.08)		10.25 (3.09)		<0.001[a]
Time from Trauma to CTB (hours)	3.57 (1.50)		3.37 (1.37)		0.204[a]
Time from CTB to Drug administration (hours)	1.00 (0.00)		1.3 (0.58)		0.471[a]
TBI Grade					
Mild		85 (50.9)		51 (30.5)	0.001[b]
Moderate		47 (28.1)		65 (38.9)	
Severe		35 (21.0)		51 (30.5)	
TBI Type					
EDH		34 (20.4)		44 (26.3)	0.428[b]
SDH		53 (31.7)		47 (28.1)	
IPH		80 (47.9)		76 (45.5)	
Clot Location					
Right		72 (43.1)		75 (44.9)	0.765[b]
Left		81 (48.5)		74 (44.3)	
Bifrontal		6 (3.6)		10 (6.0)	
Interhemispheric		6 (3.6)		7 (4.2)	
Posterior fossa		2 (1.2)		1 (0.6)	
First clot volume	5.80 (4.13)		6.80 (5.29)		
Repeated clot volume	6.98 (4.74)		7.52 (6.38)		
Operation					
No		135 (80.8)		104 (62.3)	<0.001[b]
Yes		32 (19.2)		63 (37.7)	
Blood Transfusion					
No		139 (83.2)		121 (72.5)	0.025[b]
Yes		28 (16.8)		46 (27.5)	
Side Effect DVT					
No	167 (100.0)			166 (99.4)	>0.950[c]
Yes	0 (0.0)			1 (0.6)	

Abbreviations: TXA = tranexamic acid; SD = standard deviation; GCS = Glasgow Coma Scale; CTB = computed tomography of the brain; TBI = traumatic brain injury; EDH = extradural haemorrhage; SDH = subdural haemorrhage, IPH = intraparenchymal haemorrhage; DVT = deep vein thrombosis; a = Independent T test, b = Pearson Chi-Square, c = Fisher Exact test.

Table II: Effect of tranexamic drug on outcome (GOSE score), clot expansion and mortality

	Without Drug	With Drug	χ^2 statistics (df)	p value
GOSE for TBI (overall)				
Poor	25 (15.0%)	27 (16.2%)	0.09 (1)	0.763[a]
Good	142 (85.0%)	140 (83.8%)		
	n = 167	n = 167		
GOSE for severe acute SDH				
Poor	12 (92.3%)	9 (52.9%)	-	0.042[b]
Good	1 (7.7%)	8 (47.1%)		
	n = 13	n = 17		
GOSE for moderate acute SDH				
Poor	0 (0.0%)	5 (33.3%)	-	0.042[b]
Good	14 (100.0%)	10 (66.7%)		
	n = 14	n = 15		
GOSE for severe IPH				
Poor	9 (69.2%)	10 (43.5%)	2.21 (1)	0.137[a]
Good	4 (30.8%)	13 (56.5%)		
	n = 13	n = 23		
GOSE for moderate IPH				
Poor	1 (3.8%)	0 (0.0%)	-	0.263[b]
Good	25 (96.2%)	32 (100.0%)		
	n = 26	n = 32		
Clot expansion				
Not significant	85 (61.2%)	96 (87.3%)	21.11 (1)	<0.001[a]
Significant	54 (38.8%)	14 (12.7%)		
	n = 139	n = 110		
Mortality	3 (1.8%)	5 (3.0%)	0.51 (1)	0.474[a]
	n = 167	n = 167		

Abbreviations: GOSE = Glasgow Outcome Score – Extended; SDH = subdural haemorrhage, IPH = intraparenchymal haemorrhage; a = Chi-Square test, b = Fisher Exact test.

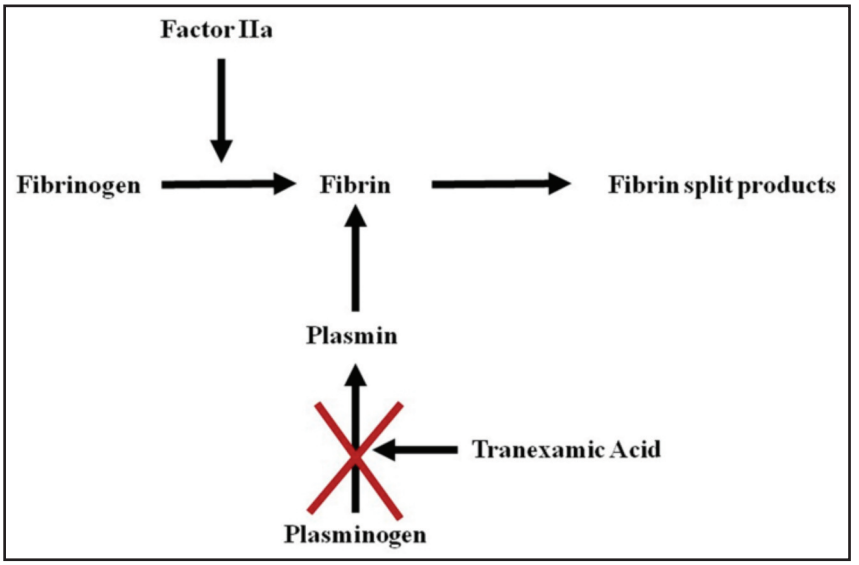

Fig. 1: The mechanism of action of tranexamic acid in the coagulation cascade.

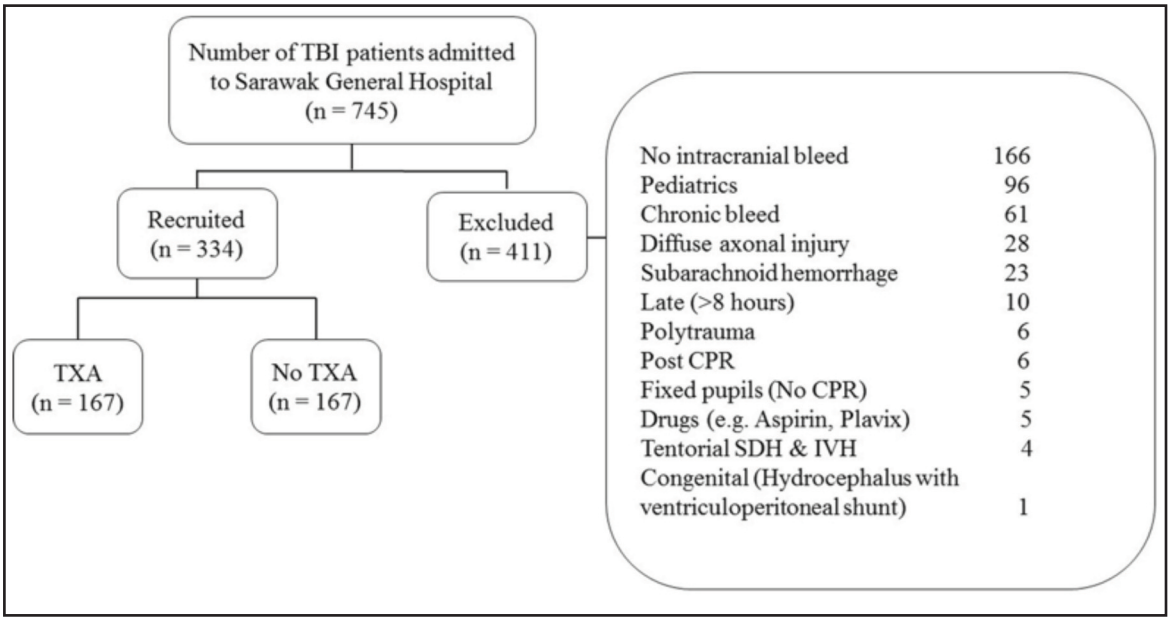

Fig. 2: Flow of participants into the study. Abbreviations: TBI = traumatic brain injury; TXA = tranexamic acid; CPR = cardiopulmonary resuscitation; SDH = subdural haemorrhage; IVH = intraventricular haemorrhage.

Table II shows the differences between the TXA group and non-TXA group in various parameters. To test the difference between TXA and non-TXA with overall GOSE score, a chi-square test was performed. In all 85% of the patients who did not receive TXA had good GOSE score while for patients who received TXA, 83.8% of them had good GOSE score. Results showed no significant difference between the two groups (p=0.763).

We further subcategorized the types and grades of TBI and analysed them (Table II). Under the TXA arm, 47.7% of the patients with severe acute SDH had good GOSE scores. For those without TXA, only 7.7% of the patients with severe acute SDH had good GOSE scores. The difference was significant (p=0.042). Similar findings were also noted for moderate acute SDH of which the difference was significant (p=0.042).

In all 56.5% of the patients with severe intraparenchymal haemorrhage (IPH) in the TXA arm had good GOSE scores as compared to 30.8% in the non-TXA group (Table II). The difference was not significant (p=0.137). The difference was also not significant in the moderate IPH subgroup (p=0.263). A total of 139 patients without TXA and 110 patients with TXA had repeated CTB. The others did not have repeated CTB because they underwent surgery immediately after the first CTB. For patients who were given TXA, 87.3% of them had no significant clot expansion. Meanwhile, for those

without TXA, only 61.2% of them had no significant clot expansion (Table II). The difference was significant (p<0.001). The clot reduction rate was 26.1% (38.8-12.17%). In our study, the rate of mortality due to all cause for patient administered with TXA was 3.0% compared to 1.8% for patients who did not receive TXA (Table II). The difference was not significant (p=0.474).

DISCUSSION

In this study the mean age difference for the two groups, those who received TXA and those who did not was insignificant hence the two groups were comparable in terms of age. The mean GCS difference was significant, and this was because there were more severe TBI patients under the TXA arm as compared to the non-TXA arm. Furthermore, for the non-TXA group, there were more mild TBI patients as compared to the TXA group. However, this did not affect the rate of clot expansion which was the focus of our study. However, despite having lower mean GCS for TXA group, they have significantly better GOSE outcomes in the moderate to severe types of acute SDH as compared to those without TXA.

Most of the patients sustained intraparenchymal haemorrhage. This concurred with the fact that cerebral contusions are the most frequently encountered lesions worldwide. In this study, there were more surgeries conducted in the patients in the TXA arm. This was because there were more patients with severe TBI in the TXA arm, hence the percentage of operation was higher than those without TXA. The percentage of blood transfusion was also higher in the TXA group. This was also because there were more patients who received TXA having severe traumatic brain injury compared to those who did not and most of them underwent surgery. It is noteworthy that, not all the patients had repeated CTB as some of them underwent surgery immediately after the first CTB. Six patients with TXA given and 4 patients without TXA had repeat CTB before operation.

There was no significant difference between TXA and non-TXA groups in terms of good GOSE score in TBI patients generally. However, by subdividing the categories of TBI, we found out that our patients with moderate to severe acute SDH that were given TXA had better outcomes than those who did not receive TXA. Mild TBI and EDH were not analysed individually as they generally have good outcomes. Despite the short course of TXA, it was noted that the 2 doses were able to reduce clot expansion significantly by about one quarter (26.1%). A fixed dose was given as it was not practical to measure the weight of a patient especially those who were admitted with severe TBI to the casualty unit. This fixed dose of 2g in total has been shown to inhibit fibrinolysis and provide haemostatic benefit. It was proven to be efficacious for patients heavier than 100kg but also safe in patients below 50kg.[14] TBI with intracranial bleed triggers the extrinsic and intrinsic pathways of coagulation cascade resulting in the formation of a fibrin clot. However, eventually, this is followed by fibrinolysis via the activation of plasminogen to plasmin.[16] Increased fibrinolysis is the main cause of coagulopathy that can lead to further worsening of the condition of patients with TBI.[22] TXA functions to prevent fibrinolysis via the deactivation of plasminogen.[23] Thus, it is prudence to administer TXA as soon as possible when a patient has intracranial bleed. In short, TXA stabilizes the clot size and prevents further worsening the condition of the patient.

One case of deep vein thrombosis (DVT) was seen in one of our patients who were given TXA (0.6%). The frequency of thrombotic even like DVT or pulmonary embolism in one report was noted to be 1.9%.[24] The safety of the drug was also shown to have no increased risk in non-fatal thrombotic events of TXA (1.7%) in the CRASH-2 trial.[14] CRASH-3 study also concluded that TXA is safe for patients with isolated TBI.[25]

In CRASH-2, all-cause mortality was significantly reduced with TXA administration.[14] However, in our study, TXA did not show a significant reduction in mortality. This is probably because TBI is a complex disease and there are many factors that can cause mortality, for instance, nosocomial infection and comorbidities in the patients.

Strength and weaknesses

We included all isolated TBI patients with intracranial bleed because we wanted to measure the clot expansion across all categories and grades of TBI. Most of the published studies only included moderate to severe TBI.[19,20] Our study ensured that clot expansions in mild TBI were not overlooked. Furthermore, most of the severe TBI patients underwent surgery and a repeat of CTB prior to surgery is not feasible as it will only further delay the treatment and put the patients at greater risk.

The weakness of this study is that the inclusion of mild TBI and patients with EDH affects the analysis of the GOSE outcome of TBI patients. This is because mild TBI patients and those with EDH commonly have good outcomes. Therefore, we analysed patients with moderate to severe TBI with acute SDH and acute IPH separately.

Difficulties and challenges

The difficulties in this study included in recruiting patients. As Sarawak in Malaysia lacks good roads, most of the patients arrive late and in severe conditions with bilateral fixed pupils or resulting in asystole and CPR. Furthermore, TBI is a complex disease and to determine the cause of death solely due to TBI is not easy. Most commonly, death is due to multiple factors which include hospital-acquired pneumonia. Besides that, the detection of DVT might not be accurate as we did not perform lower limb ultrasound for all our patients involved. Some of them may have had subclinical DVTs that was not picked up.

Safety and current standings

TXA is an affordable and widely available drug with a long track record of safety profile and effectiveness. In the past, TXA was used widely in dental surgery, general surgery, orthopaedics and obstetrics and gynaecology departments. This status may change as it is gaining popularity in other surgical departments, especially in neurosurgery. It is hoped that in future, TXA will be an essential drug in the armamentarium of neurotrauma.

CONCLUSIONS

TXA reduces the rate of clot expansion in TBI by 26.1% (12.7-38.8%) without significantly increasing the risk of a thrombotic event. It can also improve the outcome of moderate and severe TBI patients with acute subdural haemorrhage. It is a potentially life-saving treatment that should be considered in future in patients with TBI. However, a larger study is needed to ascertain the optimal drug dosage, timing and duration.

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