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Original Article

Efficacy and Safety of Tranexamic Acid in Preventing Rebleeding after Subarachnoid Hemorrhage: A Randomized Controlled Trial

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Abstract

Background: *Recent studies have indicated that early, short-course therapy with Tranexamic Acid (TXA) along with standard treatment for prevention of ischemia in aneurysmal Subarachnoid Hemorrhage (SAH) may be beneficial in preventing rebleeding and improving outcome. The study aimed to assess the efficacy and safety of short-course early administration of TXA combined with standard treatment to prevent rebleeding after SAH.*

Materials and methods: *Seventy-four patients suffering from SAH verified on Computed Tomography (CT) scan within 72 hours after the primary hemorrhage were randomized into two treatment arms [37 received TXA and standard treatment (Experimental group), 37 received standard treatments only (Control group)]. TXA 1 gm was given intravenously slowly over 10 minutes, followed by 1 gm iv eight hourly up to a maximum of 72 hours. They were followed up for one month to observe rebleeding and outcome by Glasgow Outcome Scale.*

Results: *Effective sample size was 70 (35 in TXA, 35 in the no-TXA group) due to the dropout of 4 patients. Out of 70 patients, 21 (30%) had rebleeding, and most of the rebleeding (95.23%) occurred after 72 hours of the initial event. Patients who had rebleeding had comparably lower GCS scores at presentation. Out of 21 rebleeding cases, 20 (95.23%) died within one month from the symptom onset. There was no significant difference (p=0.434) in rebleeding rate in TXA-treated patients (25.7%) versus non-TXA patients (34.3%). Treatment with TXA had no beneficial effect on one-month outcome (p>0.05).The adverse events were similar in the two groups and none of the patients had a seizure.*

Conclusions: *Early short course TXA was tolerable as add-on to standard treatment of SAH but had no significant beneficial effect in reducing rebleeding and in improving one-month outcome.*

Key words: Rebleeding; Subarachnoid hemorrhage; Tranexamic acid.

INTRODUCTION

Spontaneous Subarachnoid Hemorrhage (SAH) refers to the release of arterial blood into the subarachnoid space, usually due to an intracranial aneurysm rupture,which is a common, devastating emergency cerebrovascular disease worldwide.[1] SAH is a severe type of stroke, accounting for approximately 5% of all strokes.[2] Despite progress and development in diagnosing and treating SAH, the mortality rates are still high.[3] Increasing studies indicated that rebleeding is a leading cause of increased mortality and poor outcomes in SAH patients.[4,5] Rebleeding rates are up to 20% from ruptured aneurysms, and its highest incidence is observed in the first 24 hours after the initial hemorrhage.[6,7]

The current evidence suggests that effective aneurysm treatment as early as possible is the best way to reduce or even prevent rebleeding after a hemorrhage.[8,9] However, in a limited resource setting, it is impossible to treat patients immediately within a few hours after admission. Therefore, a more effective treatment modality, not just aneurysm surgery alone, is still needed before the aneurysm is secured. Tranexamic Acid (TXA) is a lysine analogue fixing on plasminogen to inhibit fibrinolysis and reduce bleeding. TXA has been widely used to reduce blood loss from surgery, severe traumatic injury and heavy menstruation in recent years. Its intravenous bioavailability is close to 100%, with an immediate peak plasma concentration.[10]

Numerous studies have explored the effect of TXA in SAH.[11] However, the role of tranexamic acid in promoting good clinical outcomes and reducing mortality and risk of adverse events during the treatment of SAH remains unclear. Although most studies have demonstrated that TXA can reduce rebleeding, they failed to show that it improves poor outcomes and mortality.[12,13]An increase in the risk of cerebral ischemia likely offsets the effect of TXA on rebleeding.[11,14] Given the conflicting evidence, we evaluated the efficacy and tolerability of TXA in preventing rebleeding after SAH in a randomized control trial.

MATERIALS AND METHODS

This randomized controlled trial was conducted in the Neurology Department of Chittagong Medical College Hospital from February 2017 to January 2018. The study protocol was approved by the Ethical Review Committee of Chittagong Medical College (Memo No:338). Informed written consent was obtained from the patients or attendants after a full explanation of the ultimate outcome, complications and purpose of the study. They were informed of their right to withdraw from the study at any stage.

Adult patients (Age≥18 years) were eligible for inclusion if they were admitted to the study site, had signs and symptoms (ictus) for less than 72 hours indicating SAH and had a non-contrast CT confirming SAH. Exclusion criteria were a traumatic SAH pattern on CT, ongoing treatment for deep vein thrombosis or pulmonary embolism, pregnancy, impaired renal function (Serum creatinine >1.7mg/dl), or hepatic function (ALT >150IU/L) or Glasgow Coma Scale (GCS) score <5.

Seventy-four consecutive patients were randomly assigned (1:1), as soon as possible after a non-contrast CT-proven diagnosis of SAH, to receive either TXA treatment in addition to usual care (TXA group, n=37) or care as usual only (Control group, n=37). Randomization was done by a simple lottery method. Patients of the TXA group received the standard treatment of SAH along with TXA (1gm TXAiv slowly over 10 minutes and then 1gm iv 8 hourly up to a maximum of 72 hours). Patients of the control group received standard treatment without TXA administration. Patients irrespective of the groups were advised for early surgical treatment for ruptured aneurysm.

Patients or attendants consulted with the researcher with mobile phone regarding any new symptom related to rebleeding and the researcher also communicated with them. Both groups underwent a standardized and validated interview at discharge. All events diagnosed clinically as rebleeding were tried to verify on repeat CT scans. One month after hemorrhage another interview of both groups was arranged to assess rebleeding and functional status. Main outcome variables assessed were frequency of rebleeding after SAH, adverse events and one-month outcome by Glasgow Outcome Scale (GOS).[15]

Rebleeding was defined as sudden neurological deterioration (Clinically evident by sudden onset of a severe headache which might be associated with nausea and /or vomiting, stiff neck, photophobia, brief loss of consciousness or focal neurological deficits, including cranial nerve palsies) with change in vital parameters (Possible rebleed) and presence of more SAH on CT than in a previous investigation (Definite rebleed). The World Federation of Neurological Surgeons (WFNS) scale was used for clinical grading of SAH.[16] GOS Score 4 and 5 was considered favourable outcome and GOS Score 1-3 was considered poor outcome.

Continuous variables were expressed as means with Standard Deviations (SD) and tested with the Student's t-test. The Chi-square or Fisher's exact test was used to assess differences in proportions wherever appropriate. Bivariate and multivariate logistic regression was used to determine the association between the treatment group and rebleeding, and the results were expressed as Odds Ratio (OR) with a 95% Confidence Interval (CI). p-values < 0.05 were considered significant. A per-protocol analysis was performed using the SPSS Statistics Software (Version 23.0).

RESULTS

Out of 74 randomized patients, four patients (2 from each group) were not available in the follow-ups. Reaming 70 patients were included in the final analysis. Both the groups were comparable with respect to their age and sex. There was no significant difference between the groups in their prevalence of hypertension, smoking habit, and alcohol habit.The site of the lesions in most of the cases (58.5%) was ACOMA, followed by MCA (11.4%). Only one (1.4%) patient had an ischemic deficit and 1 (1.4%) had hydrocephalus in CT findings. The earliest time of administration of TXA was 5 hours following symptom onset and 31.4% of patients received it within 24 hours and another 48.6% received it within 48 hours and the rest of the patients (20%) received it within 70 hours of symptom onset (Table I).

Table I Socio-demographic characteristics of the patients

Variables	TXA Group (n=35)		No-TXA Group (n=35)		
	n	%	n	%	p-value
Age, in years	58.03 ± 12.08		60.97 ± 13.7		0.344†
Sex					
Female	25	71.4	25	71.4	1.0*
Male	10	28.6	10	28.6	
Hypertension	28	80.0	24	68.6	0.274*
Smoking	10	28.6	12	31.4	0.094*
Alcohol habit	1	2.9	0	0.0	1.0*
Pulse (/minute)	78.3±8.8		80.4±9.0		0.32†
SBP, mmHg	164.1±22.8		175.7±33.0		0.093†
DBP, mmHg	99.3±10.4		100.9±10.7		0.536†
GCS	11.4±2.3		10.2±3.4		0.105†
Location of aneurysm					
ACOMA	20	57.2	21	60.0	
MCA	4	11.4	4	11.4	
ICA	2	5.7	2	5.7	0.481*
PCOMA	0	0.0	1	2.9	
Others	9	25.7	7	20.0	
Presence of Ischemic deficit	0	0.0	1	2.9	0.574‡
Presence of Hydrocephalus	1	2.9	0	0	0.574‡

Data were expressed as frequency (n) and percentage (%) or Mean ± SD. †Independent sample t-test, *Chi-square test, ‡Fisher's exact test. SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, GCS: Glasgow Coma Scale, ACOMA: Anterior Communicating Artery, MCA: Middle Cerebral Artery, ICA: Internal Carotid Artery, PCOMA: Posterior communicating artery. Others: Specific location of ruptured aneurysms could not be identified due to uniform extension of hemorrhage in subarachnoid space. These may be in ACOMA, MCA, ICA, PCOMA or other location.

In the TXA Group out of 35 patients, 9 (25.7%) had rebleeding and the corresponding value for the No-TXA Group was 12 (34.3%). Though the rate of rebleeding was lower in an experimental group it was not statistically significant (p=0.434). There was a nonsignificant 25% relative reduction of rebleeding in the TXA Group than in the No-TXA Group (Figure 1).

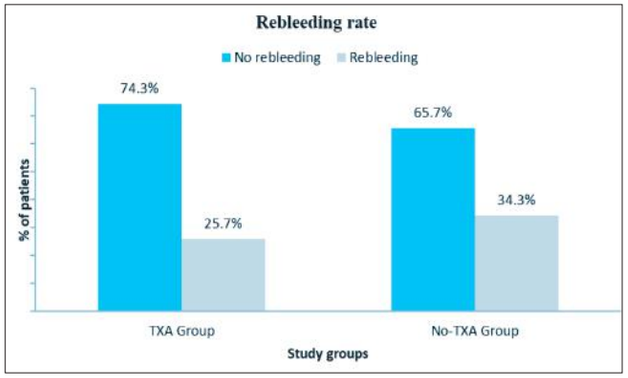

Figure 1 Incidence of rebleeding in two Groups (n=70)

Only one rebleeding occurred within 72 hours and the rest of the 20 rebleeding episodes occurred after 72 hours of symptom onset. Out of 21 rebleeding cases, 15 (71.43%) occurred among the patients who had baseline GCS 10. 20 (95.23%) cases of rebleeding died within 30 days from the symptom onset (Table II). Other than rebleeding GIT symptoms and hyponatremia were observed during the follow-up period. No patients developed or reported seizures in follow up period.

Table II Details of rebleeding by Groups (n=21)

Variables	TXA Group (n=9)		No-TXA Group (n=12)		
	n	%	n	%	p-value
Time of rebleeding					
Within 72 hours	0	0.0	1	8.3	0.794*
After 72 hours	9	100.0	11	91.7	
Relation with GCS score					
In GCS >10	5	55.55	1	8.3	0.432*
In GCS ≤10	4	44.45	11	91.7	
Relation with death					
Rebleeding & survived	0	0.0	1	8.3	0.794*
Rebleeding & died	9	100.0	11	91.7	

*Chi-square test

Some of the variables proved to have an association with rebleeding are included as independent variables in the logistic regression analysis demonstrated in Table III. The result revealed that only initial GCS at presentation is working independently in the occurrence of rebleeding.

Table III Multivariate analysis (logistic regression) with rebleeding as the dependent variable and other risk factors for rebleeding as independent variables

Variables	Adjusted RR	95% CI for (RR)	p value
GCS	0.822	0.687-0.984	0.032
Assigned Group	1.23	0.409-3.723	0.71
Interval between symptom onset to intervention	1.01	0.974-1.05	0.595
H/O Hypertension	1.45	0.395-5.32	0.576

RR: Relative Risk, CI: Confidence Interval.

There was no significant difference in one-month outcome between the two groups when assessed by the Glasgow outcome scale score. 37 (52.86%) patients died within 30 days (48.6% in TXA Group and 57.1% in No-TXA Group). 28.57% of the patients inthe TXA group had favourable 30 days outcome and the corresponding value in the No-TXA Group was 14.3% (Table IV).

Table IV Glasgow outcome scale score after 30 days by Groups

30-day outcome by GOS score	TXA Group (n=35)		No-TXA Group (n=35)		
	n	%	n	%	p-value
Favourable outcome (score ≥ 4)	10	28.57	5	14.3	0.098*
Unfavourable outcome (score <4)	25	71.43	30	85.7	

* Chi-square test

DISCUSSION

Although rebleeding is one of the major causes of morbidity and mortality among the patients of SAH, this has not been studied extensively in our setting. To fill this gap, hence, we assessed the efficacy and tolerability of short term TXA in preventing rebleeding after SAH among the patients admitted to Chittagong Medical College Hospital.

Both the groups were comparable with respect to their baseline demographic and clinical characteristics. The aneurysms were more likely to be detected in the anterior circulation than those in the posterior circulation or elsewhere in the present study, which is almost consistent with the findings of other studies.[17,18] Of the risk factors, hypertension and smoking demonstrated their significant presence among the patients studied. Other studies also showed smoking, hypertension and heavy alcohol as major modifiable risk factors.[19,20] As alcohol is prohibited both religiously and culturally, alcohol consumption is not common in our study and other study conducted in Bangladesh.[17]

Despite the current AHA/ASA guidelines encourage the use of TXA for patients who will have a delay in aneurysm obliteration, we did not find any significant reduction of rebleeding in TXA treated group in comparison to the group which had received standard treatment without TXA.[21] Our finding is contradictory to the findings of Roos et al who conducted a study to investigate whether antifibrinolytics in combination with treatment to prevent cerebral ischemia improve outcome in patients with SAH in whom occlusion of the aneurysm was delayed.[12] They noticed that TXA significantly reduced the occurrence of rebleeding. However, there are several heterogenicity between these two studies regarding sample size and dose of TXA. Starke et al also noticed a significant decrease in rebleeding in EACA-treated patients (2.7%) versus non-EACA patients (11.4%).[22] Few studies found that one gram of TXA iv every 4 hours was enough to stop fibrinolysis in the cerebrospinal fluid.[23-25] There is little reason to assume that a higher dosage or a more frequent administration of TXA would produce different results which implies that factors other than fibrinolysis alone are responsible for rebleeding after SAH.

In total, 15 (21.43%) patients had favourable 1-month outcome and 20 (28.57%) patients died of rebleeding. Out of 21 rebleeding cases, 20 (95.23%) had died. The corresponding values were 52%, 4% and 50% in the study done by Starke et al.[22]Our study was not adequately powered to detect a significant difference in the outcome. Though Roos et al found a significant reduction in rebleeding rate in the TXA group in comparison to no TXA group, antifibrinolytic treatment had no beneficial effect on outcome (RR, 1.10; 95% CI, 0.91-1.34).[12] These findings were like our study results. Similar to these findings, Hillman et al observed that the effect of TXA administration on SAH was reflected in a tendency toward a better overall outcome.[13] The GOS Scores 4 and 5 were considered favourable results, which increased from 70.5% to 74.8% but were not significant statistically. In our study, there was no significant difference in one-monthoutcome between the two groups though the trends of favourable outcome were in favour of the TXA group than their counterpart. The lack of significance for mortality rates and the overall outcome may some extent is related to the small sample size. Statistical power analysis shows that studies on very large series are needed to obtain statistical significance for the increase in a favourable outcome that was suggested by the data series of Hillman et al.[13]

After adjusting for other factors only initial GCS at presentation was found to be an independent predictor of rebleeding. Older studies suggest that rebleeding occurs in about 4% of patients during the first 24 h following initial aneurysmal SAH and 1–2% per day over the next 14 days. When very early rebleeding is also considered, the incidence of rebleeding is likely to be close to 12% in the first 24 h. Rebleeding is especially common in those patients in poor clinical condition, those with large aneurysms, those presenting with loss of consciousness or sentinel hemorrhage, and patients exposed to very early (<3 hours) angiographic workup.[26] In our study, among the 21 rebleed cases we could confirm only one case by repeat CT scan and the rest of the cases were possible rebleed diagnosed by the sudden deterioration of clinical condition and death. In our study, administration of a moderate dose of TXA for a brief period could not be linked to a higher risk of delayed ischemia or no severe thromboembolic complication was seen.

LIMITATIONS

The small sample size, the inclusion of the sample from a single hospital, and the open-label study were some important limitations of our study. Moreover, CTA or DSA could not be done to detect the morphological anatomy of the aneurysm.

CONCLUSION

In conclusion, the present study demonstrated that, though it was safe to administer early TXA in a moderate dose for 72 hours, as add-on to standard treatment of SAH, it had no significant beneficial effect in reducing rebleeding and in improving one month outcome.

RECOMMENDATION

Considering the study results and limitations it may be reasonable to administer tranexamic acid for a short period as add-on to the standard treatment of aneurysmal SAH. Nevertheless, a large, randomized, multicenter, placebo-controlled trial is needed to determine whether early antifibrinolytic therapy with TXA should be accepted as the standard of care in all patients of aneurysmal SAH.

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DISCLOSURE

All the authors declared no competing interest.

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