Tranexamic Acid in Aneurysmal Subarachnoid Hemorrhage: A Meta-analysis of Randomized Controlled Trials

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Abstract

Background

Tranexamic acid, as a hemostatic drug, is widely used to treat or prevent excessive blood loss. The efficacy of tranexamic acid in promoting good clinical outcomes, reducing mortality, and the occurrence of adverse events during treatment of aneurysmal subarachnoid hemorrhage remains unclear.

Methods

PubMed, Web of Science, Embase, and The Cochrane Library were searched for randomized-controlled trials (from 1980 to 2021) following strict inclusion and exclusion criteria. We performed STATA 16.0 and RevMan 5.3 for statistical analysis. Fixed-effect model (M-H method) and effect size RR (95% CI) were used as a pooled measure to combine the heterogeneous data. We also performed post hoc sensitivity analyses and conducted subgroup analyses to evaluate each outcome with low heterogeneity results.

Results

Meta-analysis showed that tranexamic acid was associated with reduced rebleeding (RR 0.72 [0.59, 0.87], $p = 0.0008$; $I^2: 0\%$, $p = 0.51$). Tranexamic acid probably has no effect on good clinical outcome or mortality (RR 0.98 [0.92, 1.04], $p = 0.51$; $I^2: 0\%$, $p = 0.60$; RR 1.01 [0.88, 1.15], $p = 0.91$; $I^2: 0\%$, $p = 0.51$). TXA was associated with increased hydrocephalus (RR 1.13 [1.02, 1.24], $p = 0.02$; $I^2: 0\%$, $p = 0.61$), DCI (RR 1.70 [1.34, 2.16], $p < 0.0001$; $I^2: 0\%$, $p = 0.84$) and seizure (RR 1.46 [1.00, 2.14], $p = 0.05$). The rate for thromboembolic complications were similar in both groups (RR 0.91 [0.63, 1.31], $p = 0.62$; $I^2: 0\%$, $p = 0.73$). There was significant drug related overall adverse events (RR 1.21 [1.11, 1.32], $p < 0.0001$; $I^2: 29\%$, $p = 0.14$).

Conclusions

In patients with aneurysmal subarachnoid hemorrhage, these findings indicate that it does not support the routine use of TXA.

Introduction

Aneurysmal subarachnoid hemorrhage (SAH) is a significant cause of mortality and disability worldwide, especially in the relatively young population. Over the past 30 years, the case fatality rate declined by 17%, and the incidence remained relatively stable at 9 cases per 100,000 patients per year [1]. Due to the acute onset, approximately 33% of patients died because they did not get to the hospital in time [2]. Rebleeding was closely related to the prognosis of patients with aneurysmal SAH. The earlier the rebleeding occurs, the worse the prognosis [3]. Of those who survive effective treatment, up to one in five will experience rebleeding, reducing the survival rate by 50% [4]. Tranexamic acid (TXA) is a hemostatic drug with anti-fibrinolytic activity, usually used to prevent or treat ruptured aneurysm rebleeding. In 2003,

a Cochrane Review demonstrated that TXA showed a beneficial effect on reducing rebleeding but failed to show good clinical outcomes, possibly because the benefit was offset by an increase in adverse events due to cerebral ischemia[5]. TXA with concomitant treatment strategies to prevent cerebral ischemia also showed a beneficial effect on reducing rebleeding; nonetheless, the effect of tranexamic acid on good clinical outcomes remained unclear[6]. Recently, the ULTRA, a multicenter prospective, randomized, controlled, open-label trial with 955 participants from 8 treatment centers and 16 referring hospitals, assessed the effects of ultra-early tranexamic acid for aneurysmal SAH and showed a slight reduction in mortality but not in rebleeding after randomization and before aneurysm treatment as well as in the improvement of clinical outcome at 6 months[7]. Some comments suggest that it might be associated with increased incidence of hydrocephalus and epilepsy[8, 9]. Aiming to emphasize relevant curative effects previously missed because of small samples and to better focus on adverse events during the disease treatment course, we conducted a meta-analysis to evaluate the efficacy and safety of tranexamic acid in the treatment of aneurysmal SAH.

Methods

Search strategy

We conducted a comprehensive search of PubMed, Web of Science, Embase, The Cochrane Library from January 01, 1980, until June 01, 2021, for RCTs investigating the role of TXA in patients with aneurysmal SAH. We performed the search strategy with the assistance of an expert medical librarian and included three search terms: “Tranexamic acid,” “aneurysmal subarachnoid hemorrhage,” and “Randomized Controlled Trials.” Two researchers (H.D and T.L) independently performed an initial search; discrepancies were resolved by discussion (see supplementary appendix for search string).

A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of the literature search and selection strategy of studies was presented in Fig. 1. The protocol for this systematic review was registered on PROSPERO (CRD42021251142)

Inclusion and exclusion criteria

The inclusion criteria for the systematic review and meta-analysis were as follows: (1) RCT, (2) included patients who were diagnosed with aneurysmal subarachnoid hemorrhage, (3) compared the efficacy of tranexamic acid and matching placebo, and (4) involved >25 patients, (5) the studies were published from January 1, 1980, to June 01, 2021.

The exclusion criteria were as follows: (1) studies that did not include relevant outcomes information such as mortality, good functional outcomes, or adverse events; (2) studies that were not placebo-controlled; (3) non- RCTs, such as cohort studies, reviews, or case reports.

Data extraction

According to the inclusion and exclusion criteria, Data extraction was performed by two independent authors (H.D and T.L) using standardized extraction form, which includes authors, year of publication, study design, intervention, length of TXA treatment, time from symptom onset to treatment, TXA patients/ placebo patients, key results, good clinical outcomes, rebleeding, mortality, hydrocephalus, delayed cerebral ischemia, thromboembolic complications, seizure.

The primary outcomes were good clinical outcomes, rebleeding, mortality. The mRS score was dichotomized into good clinical outcome (mRS score 0–3 [good recovery, no significant disability, slight disability, moderate disability]) or poor outcome ([mRS score 4–6 moderately severe disability, severe disability, or death]).

We also considered two other categories: poor outcome (death (GOS = 1), vegetative state (GOS = 2) or severe disability (GOS = 3)), and good clinical outcome (moderate disability (GOS = 4) or good recovery (GOS = 5)).

The secondary outcomes were adverse events defined as hydrocephalus, delayed cerebral ischemia, thromboembolic complications, seizure. Thromboembolic complications include deep venous thrombosis and pulmonary embolism.

Statistical analysis

We used STATA 16.0 (StataCorp LP) and RevMan version 5.3 software (Cochrane Collaboration) to perform the meta-analysis. We used the fixed-effect model (M-H method) and effect size RR (95% CI) as a pooled measure. Inconsistent index (I²) test, which ranges from 0 to 100%, was used for assessing homogeneity among the studies, and both $P \geq 0.1$ and $I^2 \leq 50\%$ were considered no heterogeneity among the studies. Two independent reviews adopted the Cochrane risk of bias tool to assess the risk of bias for RCTs[10]. Risk of bias tool refers: random sequence generation(A); allocation concealment(B); blinding of participants and personnel(C); blinding of outcome assessments(D); incomplete outcome data addressed(E); selective outcome reporting(F); other potential threats(G), respectively.

A small study effect was tested using a regression-based test (Harbord test) for binary outcomes. Regression-based Egger's test was also performed for the risk of publication bias. We also performed post hoc sensitivity analyses and conducted subgroup analyses to evaluate each outcome with low heterogeneity results. All *p* values were two-tailed with a statistical significance at 0.05 or below.

Results

Description of included studies

A total of 537 studies were identified by searching the database. After the deletion of duplicates, reviews, and irrelevant studies, 348 studies met the criteria. By evaluating titles and abstracts, 167 studies were excluded. After assessing 22 full-text for eligibility, we excluded 15 because 1)no control group(n=7), 2)case report, 3)non-RCT studies (n=7). Therefore, seven articles were included in the qualitative

synthesis[7, 11-16]. A total of 2917 patients from 7 RCTs were randomly assigned to TXA treatment (n = 1403) or placebo (n = 1514) for meta-analysis. Each group included 29 to 480 patients. The largest RCT population was a multicenter study published in 2021[7]. Three studies were open-label RCTs[7, 11, 16], while the remaining four were double-blind RCTs[12-15]. The subjects were all adults. Time from symptom onset to treatment varied among studies: within 72 hours in 4 trials[11, 13-15], within 96 hours in 1 trial[12], in the latest trial, TXA was given within 24 hours after symptom onset[7], and another was not reported[16]. The length of TXA treatment also varied, ranging from 24 hours to 6 weeks. Baseline characteristics of included trials are summarized in Table 1. Details of the risk of bias summary were presented in Fig. 2 and Fig. 3.

Table 1 Characteristics of the included studies

Primary outcomes

The incidence of rebleeding was clarified in all RCTs; the forest plot for rebleeding is shown in Fig. S1A. Of 1403 patients, 162 (11.5%) who received TXA exhibited rebleeding, while 301 of 1514 patients (19.9%) exhibited rebleeding in the placebo group. There was significant difference in incidence of rebleeding between TXA and placebo (RR 0.60 [0.51, 0.71], $p < 0.00001$; I^2 : 62%, $p = 0.02$; Fig. S1A). Six studies reported data on good clinical outcomes for the efficacy of TXA in patients with aneurysmal SAH. The good clinical outcome was not significantly different between TXA and placebo groups (RR 0.98 [0.92, 1.04], $p = 0.51$; I^2 : 0%, $p = 0.60$; Fig. S1B). Mortality from any cause was evaluated in six RCTs. With these six RCTs analyzed, the forest plot was shown in Fig. S1C. 325 patients (27.7%) died in the TXA-treated group, while 356 patients (27.8%) died in the placebo group. Pooled analysis found that TXA likely had no effect on mortality (RR 1.03 [0.91, 1.17], $p = 0.63$; I^2 : 12%, $p = 0.34$; Fig. S1C).

Secondary outcomes

We found difference of adverse events (a composite prognosis defined by our authors), Pooled results demonstrated probably increased risk of hydrocephalus (RR 1.13 [1.02, 1.24], $p = 0.02$; I^2 : 0%, $p = 0.61$; Fig. S2A), delayed cerebral ischemia (RR 1.21 [1.05, 1.39], $p = 0.01$; I^2 : 60%, $p = 0.02$; Fig. S2B), and seizure (RR 1.46 [1.00, 2.14], $p = 0.05$; Fig. S2D). However, there was an uncertain effect of TXA on thromboembolic complications (RR 0.79 [0.56, 1.12], $p = 0.18$; I^2 : 28%, $p = 0.24$; Fig. S2C). There was significant drug related overall adverse events (RR 1.14 [1.06, 1.24], $p = 0.0009$; I^2 : 39%, $p = 0.05$; Fig. S2).

Subgroup analysis for randomized controlled trials with low heterogeneity

In this pooled analysis with low heterogeneity, Part of the studies were excluded due to a higher heterogeneity. Meta-analysis showed that TXA was associated with decreased rebleeding (RR 0.72 [0.59, 0.87], $p = 0.0008$; I^2 : 0%, $p = 0.51$; Fig. 1A), increased hydrocephalus (RR 1.13 [1.02, 1.24], $p = 0.02$; I^2 : 0%, $p = 0.61$; Fig. 2A), DCI (RR 1.70 [1.34, 2.16], $p < 0.0001$; I^2 : 0%, $p = 0.84$; Fig. 2B) and Seizure (RR 1.46 [1.00, 2.14], $p = 0.05$; Fig. 2D). The good clinical outcome and mortality was similar in both groups (RR 0.98

Authors	Study design	Intervention	Length Of TXA treatment	Time from symptom onset to treatment (hours)	TXA patients/ placebo patients	Key results
René Post et al, 2021	Open-label RCT	1g bolus, followed by 1 g every 8 h, placebo	24 hours	<24 hours	480/475	TXA did not improve clinical outcome in patients with aneurysmal SAH at 6 months.
Y. Roos et al, 2000	Double-blind RCT	6g/d(1g/4 h) during the week 1, and 6 g/d (1.5g/6 h) in week 2 and 3	3 weeks	<96 hours	229/233	TXA had no beneficial effect on outcome. It decreases the risk of rebleeding and did not increase ischemic events.
Hillman et al, 2002	Open-label RCT	1g intravenously , followed by 1 g every 6 hours	<72 hours	<72 hours	254/251	There were no indications of increased risk of either ischemic manifestations or vasospasm that could be linked to TXA treatment.
Vermeulen et al, 1984	Double-blind RCT	6 g/day i.v. in week 1 and 2, 4 g/day i.v. or 6 g/day orally in week 3 and 4	4 weeks	<72 hours	241/238	TXA significantly increased the risk of cerebral ischemia and decreases rebleeding. No impact on mortality and functional outcome. No impact on hydrocephalus.
Fodstad et al, 1981	Open-label RCT	6 g/day in week 1 and 3-6, 4 g/day in week 2	6 weeks	NR	30/29	TXA increased the risk of cerebral infarction, and decreased the risk of hydrocephalus.
Eelco et al, 1989	Double-blind RCT	6 g/day were given for a maximum of 96 hours	4 day	<72 hours	119/238	TXA failed to reduce the incidence of rebleeding but still increased the rate of cerebral infarction.

Tsementzis et al, 1990	Double-blind RCT	6 g/day in week 1 and 4 g/day in week 2, 3 and 4.	4 weeks	<72 hours	50/50	TXA significantly increased ischemic complications. No impact on mortality, outcome, and rebleeding.
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[0.92,1.04], $p = 0.51$; $I^2: 0\%$, $p = 0.60$; Fig. 1B; RR 1.01 [0.88,1.15], $p = 0.91$; $I^2: 0\%$, $p = 0.51$; Fig. 1C). The risk for TC were similar in both TXA and placebo group (RR 0.91 [0.63, 1.31], $p = 0.62$; $I^2: 0\%$, $p = 0.73$; Fig. 2C). TXA was associated with increased overall adverse events (RR 1.21 [1.11, 1.32], $p < 0.0001$; $I^2: 29\%$, $p = 0.14$; Fig. 2). Regression-based Harbord's test and Egger's test were not statistically significant for primary and secondary outcomes (Table 2).

Table 2 Summary of Meta-analysis

CI Confidence Interval DCI Delayed Cerebral Ischaemia TC Thromboembolic Complications

^a indicated Hillman et al. and Vermeule et al. were excluded. ^b indicated Tsementzis et al. was excluded. ^c indicates René Post et al. and Y. Roos et al were excluded. ^d indicated Eelco et al. was excluded.

Discussion

Our study provides a comprehensive overview to clarify the efficacy and safety of TXA administration compared to that of placebo in aneurysmal SAH patients. Although previous systematic reviews of TXA treatment in aneurysmal SAH patients have been published, however, in these meta-analyses, the largest randomized controlled trial, the ULTRA-trial, was not included in the literature search. Our results demonstrate that TXA probably has a significant effect on rebleeding and an uncertain effect on good clinical outcomes and mortality when administered to patients with aneurysmal SAH. The prevalence rates of adverse events among aneurysmal SAH patients showed a significant difference, except thromboembolic complications. TXA treatment demonstrated a tendency to increase the risk of adverse events such as hydrocephalus, DCI, seizure in the aneurysmal SAH population. Overall, our study might help acquaint the efficacy and safety of TXA on aneurysmal SAH.

Rebleeding is the leading cause of death for intracranial aneurysms patients, with an incidence of 10-22%; the onset appeared in the first 24 h, peaking in the first 3-6 h after the event[17, 18]. Many RCTs have shown that TXA treatment could considerably reduce the risk of rebleeding[11-13, 15, 16], the curative effect is closely related to its pharmacological action[19, 20]. TXA can inhibit fibrinolysis by replacing plasminogen from fibrin and also inhibits enzymatic degradation by plasmin[21, 22]. Nevertheless, in the recent publication of the ULTRA, rebleeding after randomization and before aneurysm treatment occurred in the tranexamic acid and control group did not reach the predefined threshold for statistical significance, perhaps because half of the rebleeding occurred within 3 hours, in this trial, the

Outcomes	Model (OR/RR)	(95% CI), <i>p</i> - value	Heterogeneity (<i>I</i> ²) , <i>p</i> -value	Harbord's Test, Egger's Test	NO. of Studies
Rebleeding	Fixed (RR)	0.60[0.51,0.71], <0.00001	62%, 0.02	0.829, 0.719	7
Good Clinical Outcomes	Fixed (RR)	0.98[0.92,1.04], 0.51	0%, 0.60	0.779, 0.781	6
Mortality	Fixed (RR)	1.03[0.91,1.17], 0.63	12%, 0.34	0.320, 0.313	6
Hydrocephalus	Fixed (RR)	1.13[1.02,1.24], 0.02	0%, 0.61	0.554, 0.534	6
DCI	Fixed (RR)	1.21[1.05,1.39], 0.01	60%, 0.02	0.016, 0.017	7
TC	Fixed (RR)	0.79[0.56,1.12], 0.18	28%, 0.24	0.348, 0.190	4
Seizure	Fixed (RR)	1.46[1.00,2.14], 0.05	-	-	1
Pooled analysis with low heterogeneity					
Rebleeding ^a	Fixed (RR)	0.72[0.59,0.87], 0.0008	0%, 0.51	0.324, 0.338	5
Good Clinical Outcomes	Fixed (RR)	0.98[0.92,1.04], 0.51	0%, 0.60	0.779, 0.781	6
Mortality ^b	Fixed (RR)	1.01[0.88,1.15], 0.91	0%, 0.51	0.892, 0.886	5
Hydrocephalus	Fixed (RR)	1.13[1.02,1.24], 0.02	0%, 0.61	0.554, 0.534	6
DCI ^c	Fixed (RR)	1.70[1.34,2.16], <0.0001	0%, 0.84	0.855, 0.810	5
TC ^d	Fixed (RR)	0.91[0.63,1.31], 0.62	0%, 0.73	0.858, 0.855	3
Seizure.	Fixed (RR)	1.46[1.00,2.14], 0.05	-	-	1

median interval time from symptomatic onset to treatment was 3 hours, a considerable proportion of rebleeds had occurred. Another factor may be that the usual practice is to eliminate the aneurysm as early as possible, preferably within 24 hours[23]. The average time from diagnosis to treatment of the aneurysm in this trial was 14 hours. This early aneurysm treatment may be more critical than TXA in reducing rebleeding compared to previous trials.

The efficacy of TXA in reducing rebleeding has been proven, and studies also reported that TXA might have anti-inflammatory and healing effects[24, 25]. Theoretically, these polytropic effects might lead to good clinical outcomes, but they do not. Although previous trials investigating long-term (throughout the hospital admission) or short-term TXA treatment in patients with SAH showed a reduction in rebleeding, they failed to show a beneficial effect on clinical outcome[6, 14, 18]. Conversely, the combination with chlorpromazine or using higher doses can lead to worse outcomes[16, 26]. In the ULTRA trial, TXA was associated with a lower rate of excellent clinical outcome (mRS 0–2 at 6 months), although it did not positively affect good clinical outcomes (mRS 0-3 at 6 months). Fortunately, there was no difference in all-cause mortality at 30 days and 6 months between the two groups[7]. In 2002, Hillman et al. showed a significant reduction in mortality rate due to rebleeding by 80% upon TXA treatment[11]. Nonetheless, the mortality of TXA in patients with aneurysmal SAH is controversial, with conflicting trial results[7, 12-16, 18]. Thus, we hypothesize that not-predefined adverse events, e.g., hydrocephalus or other complications, might have played a role in contributing to poor outcomes, either alone or in combination.

Whether the harm might outweigh the potential benefits of TXA remains controversial[5, 6]. Roos et al. presented evidence that clinical outcome was offset by an increase in poor outcomes caused by cerebral ischemia[5]. An updated review showed that TXA should not be routinely used to treat aneurysmal SAH, even in patients who had concomitant treatment strategy to prevent DCI, and no sufficient evidence concluded that TXA reduced the risk of either cerebral ischemia or hydrocephalus [6]. Studies have suggested an increased cerebral ischemia rate or cerebral infarctions when using TXA[27-30]. Therefore, the current European guideline reached no international consensus on the use of TXA following SAH[31].

In contrast, comparing TXA-treated nontraumatic SAH patients with controls, Thorkil et al. demonstrated no substantial indication of increased risk of ischemic lesions[32]. American guidelines found it reasonable to use a short-term(<72 hours) TXA in aneurysmal SAH patients[23]. However, the efficacy of reducing the risk of rebleeding was reduced [7, 14]. Hydrocephalus is a common adverse event after aneurysmal SAH[33, 34]. In cases of clinical deterioration because of acute hydrocephalus, ultra-early treatment might improve clinical symptoms but increase the risk of a poor prognosis[35, 36]. Mainly because the most frequent adverse events after ventricular drainage were rebleeding[37, 38]. In our meta-analysis, the confidence intervals of hydrocephalus indicate that TXA exerts potential harm on aneurysmal SAH patients.

Contrary to other RCTs[39-42], Chakroun et al. demonstrated that TXA increased the incidence of pulmonary embolism in patients with traumatic brain injury[43]. Another retrospective study of 687 wounded soldiers showed that TXA did increase the risk of venous thrombosis[44]. In contrast, a meta-analysis of 30,522 patients in 7 clinical RCTs showed that, despite no statistical difference, the incidence of vascular occlusion in the TXA group was lower than that in the control group[45]. Shoji et al. confirmed that although thromboembolic complications such as pulmonary embolism and deep vein thrombosis may occur, the probability is relatively low[46]. Our study also found no difference in the incidence of Thromboembolic complications between the two groups.

During the first few days following subarachnoid hemorrhage, cisternal blood may have an irritative effect on the cerebral cortex, leading to a seizure; rebleeding was also associated with epileptic seizures[47, 48]. However, the mechanism between TXA and epileptic seizures is still not precise; some studies suggested that it might be the direct effect of TXA on the central nervous system; for example, TXA applied to the cortex or injected into the cisterna magna could cause grand mal epilepsy [48-50]. It also suggested that TXA increases the excitability of the central nervous system by inhibiting Gamma-aminobutyric acid A receptors[51]. Hisato et al. found that TXA was associated with a 4.1-fold increase in epileptic seizure risk in adult cardiac surgery patients compared to controls[52]. Susan et al. reported in 2020 that 2gTXA increased the risk of epilepsy in patients with moderate to severe TBI by 2.5 times compared with the control group; in patients with moderate to severe traumatic brain injury without parenchymal bleeding, the risk of epilepsy increased by 3 times. However, there was no statistical difference[53]. Only one study reported the incidence of epilepsy; the study showed a statistically significant difference in epilepsy[7]. Therefore, when TXA is applied, the occurrence of epilepsy should be vigilant, and the electroencephalogram should be perfected if necessary.

This meta-analysis has some strengths. First, we implemented comprehensive search strategies in different databases; meanwhile, our study provides a comprehensive overview to clarify the efficacy and safety of TXA administration in aneurysmal SAH patients. Second, in summarizing all of the published data on rebleeding, good clinical outcomes, mortality, delayed cerebral ischemia, we further investigated whether TXA use is associated with increased incidences of hydrocephalus and seizures. Third, we conducted a sensitivity analysis to carry out subgroup analysis for RCTs, strengthening our meta-analysis.

This study also has several limitations. First, our broad inclusion criteria led to a heterogeneous population with a range of reasons for the length of TXA treatment, Intervention dose, time from symptom onset to treatment, and disease severities, which might lead to potential bias when evaluating the efficacy and safety of TXA. Second, the ULTRA trial study population represents nearly a third of the included population in our meta-analysis, which can be considered an overrepresentation. Third, different prognostic indicators were used (mRS, GOS), there was relative uncertainty regarding all the estimates. Finally, the inherent limitations of meta-analysis, such as publication bias, cannot be ignored.

Conclusion

This meta-analysis of 7 RCTs demonstrates that TXA can reduce rebleeding but a similar effect on good clinical outcomes and mortality in aneurysmal SAH patients. Meanwhile, this treatment conveys an increased risk of hydrocephalus, delayed cerebral ischemia, and seizure, which limits the value of its clinical application, but the incidence of thromboembolic complications was similar in both TXA and placebo groups. These findings indicate that it does not support the routine use of TXA in the patients with aneurysmal SAH.

Abbreviations

RCT: Randomized Controlled Trials, TXA: Tranexamic Acid; SAH: Subarachnoid Hemorrhage; TC: Thromboembolic Complications; DCI: Delayed Cerebral Ischemia; mRS: modified Rankin Scale; GOS: Glasgow Outcome Scale

Declarations

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Availability of data and materials

The datasets are available from co-authors on reasonable request.

Authors' contributions

TL and RX collected information and wrote articles. TL and HD designed the research and modified the article. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

References

1. de Rooij NK, Linn FH, van der Plas JA, Algra A, Rinkel GJ. Incidence of subarachnoid haemorrhage: a systematic review with emphasis on region, age, gender and time trends. *J Neurol Neurosurg Psychiatry*. 2007;78 12:1365-72; doi: 10.1136/jnnp.2007.117655.
2. Rinkel GJ, Algra A. Long-term outcomes of patients with aneurysmal subarachnoid haemorrhage. *Lancet Neurol*. 2011;10 4:349-56; doi: 10.1016/s1474-4422(11)70017-5.

3. Tanno Y, Homma M, Oinuma M, Kodama N, Ymamamoto T. Rebleeding from ruptured intracranial aneurysms in North Eastern Province of Japan. A cooperative study. *J Neurol Sci.* 2007;258 1-2:11-6; doi: 10.1016/j.jns.2007.01.074.
4. Larsen CC, Astrup J. Rebleeding after aneurysmal subarachnoid hemorrhage: a literature review. *World Neurosurg.* 2013;79 2:307-12; doi: 10.1016/j.wneu.2012.06.023.
5. Roos YB, Rinkel GJ, Vermeulen M, Algra A, van Gijn J. Antifibrinolytic therapy for aneurysmal subarachnoid haemorrhage. *Cochrane Database Syst Rev.* 2003; 2:Cd001245; doi: 10.1002/14651858.Cd001245.
6. Baharoglu MI, Germans MR, Rinkel GJ, Algra A, Vermeulen M, van Gijn J, et al. Antifibrinolytic therapy for aneurysmal subarachnoid haemorrhage. *Cochrane Database Syst Rev.* 2013; 8:Cd001245; doi: 10.1002/14651858.CD001245.pub2.
7. Post R, Germans MR, Tjerkstra MA, Vergouwen MDI, Jellema K, Koot RW, et al. Ultra-early tranexamic acid after subarachnoid haemorrhage (ULTRA): a randomised controlled trial. *Lancet.* 2021;397 10269:112-8; doi: 10.1016/s0140-6736(20)32518-6.
8. Lo BWY, Fukuda H, Tsang ACO, Langer DJ, Miyawaki S, Koyanagi M, et al. Commentary on Post, et al. Ultra-early tranexamic acid after subarachnoid hemorrhage: A randomized controlled trial. *Lancet* 2021. *Surg Neurol Int.* 2021;12:156; doi: 10.25259/sni_242_2021.
9. Eastin TR, Snipes CD, Seupaul RA. Are antifibrinolytic agents effective in the treatment of aneurysmal subarachnoid hemorrhage? *Ann Emerg Med.* 2014;64 6:658-9; doi: 10.1016/j.annemergmed.2014.06.004.
10. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Bmj.* 2011;343:d5928; doi: 10.1136/bmj.d5928.
11. Hillman J, Fridriksson S, Nilsson O, Yu Z, Saveland H, Jakobsson KE. Immediate administration of tranexamic acid and reduced incidence of early rebleeding after aneurysmal subarachnoid hemorrhage: a prospective randomized study. *J Neurosurg.* 2002;97 4:771-8; doi: 10.3171/jns.2002.97.4.0771.
12. Roos Y. Antifibrinolytic treatment in subarachnoid hemorrhage: a randomized placebo-controlled trial. STAR Study Group. *Neurology.* 2000;54 1:77-82; doi: 10.1212/wnl.54.1.77.
13. Tsementzis SA, Hitchcock ER, Meyer CH. Benefits and risks of antifibrinolytic therapy in the management of ruptured intracranial aneurysms. A double-blind placebo-controlled study. *Acta Neurochir (Wien).* 1990;102 1-2:1-10; doi: 10.1007/bf01402177.
14. Wijdicks EF, Hasan D, Lindsay KW, Brouwers PJ, Hatfield R, Murray GD, et al. Short-term tranexamic acid treatment in aneurysmal subarachnoid hemorrhage. *Stroke.* 1989;20 12:1674-9; doi: 10.1161/01.str.20.12.1674.

15. Vermeulen M, Lindsay KW, Murray GD, Cheah F, Hijdra A, Muizelaar JP, et al. Antifibrinolytic treatment in subarachnoid hemorrhage. *N Engl J Med*. 1984;311 7:432-7; doi: 10.1056/nejm198408163110703.
16. Fodstad H, Forssell A, Liliequist B, Schannong M. Antifibrinolysis with tranexamic acid in aneurysmal subarachnoid hemorrhage: a consecutive controlled clinical trial. *Neurosurgery*. 1981;8 2:158-65; doi: 10.1227/00006123-198102000-00004.
17. Germans MR, Coert BA, Vandertop WP, Verbaan D. Time intervals from subarachnoid hemorrhage to rebleed. *J Neurol*. 2014;261 7:1425-31; doi: 10.1007/s00415-014-7365-0.
18. Post R, Germans MR, Boogaarts HD, Ferreira Dias Xavier B, Van den Berg R, Coert BA, et al. Short-term tranexamic acid treatment reduces in-hospital mortality in aneurysmal sub-arachnoid hemorrhage: A multicenter comparison study. *PLoS One*. 2019;14 2:e0211868; doi: 10.1371/journal.pone.0211868.
19. Carley S, Sen A. Best evidence topic report. Antifibrinolytics for the initial management of sub arachnoid haemorrhage. *Emerg Med J*. 2005;22 4:274-5; doi: 10.1136/emj.2005.023523.
20. Chwajol M, Starke RM, Kim GH, Mayer SA, Connolly ES. Antifibrinolytic therapy to prevent early rebleeding after subarachnoid hemorrhage. *Neurocrit Care*. 2008;8 3:418-26; doi: 10.1007/s12028-008-9088-5.
21. Vel R, Udupi BP, Satya Prakash MV, Adinarayanan S, Mishra S, Babu L. Effect of low dose tranexamic acid on intra-operative blood loss in neurosurgical patients. *Saudi J Anaesth*. 2015;9 1:42-8; doi: 10.4103/1658-354x.146304.
22. Mahdy AM, Webster NR. Perioperative systemic haemostatic agents. *Br J Anaesth*. 2004;93 6:842-58; doi: 10.1093/bja/aeh227.
23. Connolly ES, Jr., Rabinstein AA, Carhuapoma JR, Derdeyn CP, Dion J, Higashida RT, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/american Stroke Association. *Stroke*. 2012;43 6:1711-37; doi: 10.1161/STR.0b013e3182587839.
24. Jimenez JJ, Iribarren JL, Lorente L, Rodriguez JM, Hernandez D, Nassar I, et al. Tranexamic acid attenuates inflammatory response in cardiopulmonary bypass surgery through blockade of fibrinolysis: a case control study followed by a randomized double-blind controlled trial. *Crit Care*. 2007;11 6:R117; doi: 10.1186/cc6173.
25. Teng Y, Feng C, Liu Y, Jin H, Gao Y, Li T. Anti-inflammatory effect of tranexamic acid against trauma-hemorrhagic shock-induced acute lung injury in rats. *Exp Anim*. 2018;67 3:313-20; doi: 10.1538/expanim.17-0143.

26. Fodstad H, Nilsson IM. Coagulation and fibrinolysis in blood and cerebrospinal fluid after aneurysmal subarachnoid haemorrhage: effect of tranexamic acid (AMCA). *Acta Neurochir (Wien)*. 1981;56 1-2:25-38; doi: 10.1007/bf01400969.
27. Adams HP, Jr., Kassell NF, Torner JC, Haley EC, Jr. Predicting cerebral ischemia after aneurysmal subarachnoid hemorrhage: influences of clinical condition, CT results, and antifibrinolytic therapy. A report of the Cooperative Aneurysm Study. *Neurology*. 1987;37 10:1586-91; doi: 10.1212/wnl.37.10.1586.
28. Hijdra A, van Gijn J, Nagelkerke NJ, Vermeulen M, van Crevel H. Prediction of delayed cerebral ischemia, rebleeding, and outcome after aneurysmal subarachnoid hemorrhage. *Stroke*. 1988;19 10:1250-6; doi: 10.1161/01.str.19.10.1250.
29. Pinna G, Pasqualin A, Vivenza C, Da Pian R. Rebleeding, ischaemia and hydrocephalus following anti-fibrinolytic treatment for ruptured cerebral aneurysms: a retrospective clinical study. *Acta Neurochir (Wien)*. 1988;93 3-4:77-87; doi: 10.1007/bf01402885.
30. Vergouwen MD, Vermeulen M, van Gijn J, Rinkel GJ, Wijdicks EF, Muizelaar JP, et al. Definition of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage as an outcome event in clinical trials and observational studies: proposal of a multidisciplinary research group. *Stroke*. 2010;41 10:2391-5; doi: 10.1161/strokeaha.110.589275.
31. Steiner T, Juvela S, Unterberg A, Jung C, Forsting M, Rinkel G. European Stroke Organization guidelines for the management of intracranial aneurysms and subarachnoid haemorrhage. *Cerebrovasc Dis*. 2013;35 2:93-112; doi: 10.1159/000346087.
32. Anker-Moller T, Trolborg A, Sunde N, Hvas AM. Evidence for the Use of Tranexamic Acid in Subarachnoid and Subdural Hemorrhage: A Systematic Review. *Seminars in Thrombosis and Hemostasis*. 2017;43 7:750-8; doi: 10.1055/s-0037-1604089.
33. Mehta V, Holness RO, Connolly K, Walling S, Hall R. Acute hydrocephalus following aneurysmal subarachnoid hemorrhage. *Can J Neurol Sci*. 1996;23 1:40-5; doi: 10.1017/s0317167100039160.
34. Hasan D, Vermeulen M, Wijdicks EF, Hijdra A, van Gijn J. Management problems in acute hydrocephalus after subarachnoid hemorrhage. *Stroke*. 1989;20 6:747-53; doi: 10.1161/01.str.20.6.747.
35. McIver JI, Friedman JA, Wijdicks EF, Piepgras DG, Pichelmann MA, Toussaint LG, 3rd, et al. Preoperative ventriculostomy and rebleeding after aneurysmal subarachnoid hemorrhage. *J Neurosurg*. 2002;97 5:1042-4; doi: 10.3171/jns.2002.97.5.1042.
36. Chen S, Luo J, Reis C, Manaenko A, Zhang J. Hydrocephalus after Subarachnoid Hemorrhage: Pathophysiology, Diagnosis, and Treatment. *Biomed Res Int*. 2017;2017:8584753; doi: 10.1155/2017/8584753.

37. Fountas KN, Kapsalaki EZ, Machinis T, Karampelas I, Smisson HF, Robinson JS. Review of the literature regarding the relationship of rebleeding and external ventricular drainage in patients with subarachnoid hemorrhage of aneurysmal origin. *Neurosurg Rev.* 2006;29 1:14-8; discussion 9-20; doi: 10.1007/s10143-005-0423-4.
38. Paré L, Delfino R, Leblanc R. The relationship of ventricular drainage to aneurysmal rebleeding. *J Neurosurg.* 1992;76 3:422-7; doi: 10.3171/jns.1992.76.3.0422.
39. Yutthakasemsunt S, Kittiwatanagul W, Piyavechvirat P, Thinkamrop B, Phuenpathom N, Lumbiganon P. Tranexamic acid for patients with traumatic brain injury: a randomized, double-blinded, placebo-controlled trial. *BMC Emerg Med.* 2013;13:20; doi: 10.1186/1471-227x-13-20.
40. Fakharian E, Abedzadeh-Kalahroudi M, Atoof F. Effect of Tranexamic Acid on Prevention of Hemorrhagic Mass Growth in Patients with Traumatic Brain Injury. *World Neurosurg.* 2018;109:e748-e53; doi: 10.1016/j.wneu.2017.10.075.
41. Brenner A, Belli A, Chaudhri R, Coats T, Frimley L, Jamaluddin SF, et al. Understanding the neuroprotective effect of tranexamic acid: an exploratory analysis of the CRASH-3 randomised trial. *Crit Care.* 2020;24 1:560; doi: 10.1186/s13054-020-03243-4.
42. Williams-Johnson JA, McDonald AH, Strachan GG, Williams EW. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2) A randomised, placebo-controlled trial. *West Indian Med J.* 2010;59 6:612-24.
43. Chakroun-Walha O, Samet A, Jerbi M, Nasri A, Talbi A, Kanoun H, et al. Benefits of the tranexamic acid in head trauma with no extracranial bleeding: a prospective follow-up of 180 patients. *Eur J Trauma Emerg Surg.* 2019;45 4:719-26; doi: 10.1007/s00068-018-0974-z.
44. Walker PF, Bozzay JD, Johnston LR, Elster EA, Rodriguez CJ, Bradley MJ. Outcomes of tranexamic acid administration in military trauma patients with intracranial hemorrhage: a cohort study. *BMC Emerg Med.* 2020;20 1:39; doi: 10.1186/s12873-020-00335-w.
45. July J, Pranata R. Tranexamic acid is associated with reduced mortality, hemorrhagic expansion, and vascular occlusive events in traumatic brain injury - meta-analysis of randomized controlled trials. *BMC Neurol.* 2020;20 1:119; doi: 10.1186/s12883-020-01694-4.
46. Lawati KA, Sharif S, Maqbal SA, Rimawi HA, Petrosioniak A, Belley-Cote EP, et al. Efficacy and safety of tranexamic acid in acute traumatic brain injury: a systematic review and meta-analysis of randomized-controlled trials. *Intensive Care Med.* 2021;47 1:14-27; doi: 10.1007/s00134-020-06279-w.
47. Hasan D, Schonck RS, Avezaat CJ, Tanghe HL, van Gijn J, van der Lugt PJ. Epileptic seizures after subarachnoid hemorrhage. *Ann Neurol.* 1993;33 3:286-91; doi: 10.1002/ana.410330310.

48. Lanzino G, D'Urso PI, Suarez J. Seizures and anticonvulsants after aneurysmal subarachnoid hemorrhage. *Neurocrit Care*. 2011;15 2:247-56; doi: 10.1007/s12028-011-9584-x.
49. Schlag MG, Hopf R, Zifko U, Redl H. Epileptic seizures following cortical application of fibrin sealants containing tranexamic acid in rats. *Acta Neurochir (Wien)*. 2002;144 1:63-9; doi: 10.1007/s701-002-8275-z.
50. Lecker I, Wang DS, Whissell PD, Avramescu S, Mazer CD, Orser BA. Tranexamic acid-associated seizures: Causes and treatment. *Ann Neurol*. 2016;79 1:18-26; doi: 10.1002/ana.24558.
51. Furtmüller R, Schlag MG, Berger M, Hopf R, Huck S, Sieghart W, et al. Tranexamic acid, a widely used antifibrinolytic agent, causes convulsions by a gamma-aminobutyric acid(A) receptor antagonistic effect. *J Pharmacol Exp Ther*. 2002;301 1:168-73; doi: 10.1124/jpet.301.1.168.
52. Takagi H, Ando T, Umemoto T. Seizures associated with tranexamic acid for cardiac surgery: a meta-analysis of randomized and non-randomized studies. *J Cardiovasc Surg (Torino)*. 2017;58 4:633-41; doi: 10.23736/s0021-9509.17.09877-9.
53. Rowell SE, Meier EN, McKnight B, Kannas D, May S, Sheehan K, et al. Effect of Out-of-Hospital Tranexamic Acid vs Placebo on 6-Month Functional Neurologic Outcomes in Patients With Moderate or Severe Traumatic Brain Injury. *Jama*. 2020;324 10:961-74; doi: 10.1001/jama.2020.8958.

Figures

Figure 1

Literature search and study selection strategy.

Figure 2

Forest plot comparing the rebleeding(A), good clinical outcomes(B), and all-cause mortality (C) between the TXA and placebo groups.

Figure 3

Forest plot of the meta-analysis of adverse events between TXA and placebo. A, B, D demonstrated a higher incidence, including hydrocephalus, delayed cerebral ischemia, and seizure. C showed thromboembolic complications were similar in both groups.

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