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REVIEW ARTICLE

Tranexamic acid applications in neurocritical patients: A narrative review

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Abstract In patients with spontaneous or traumatic intracranial hemorrhage, hematoma expansion is associated with poorer neurological outcomes and increased mortality. The administration of an antifibrinolytic agent like tranexamic acid (TXA) may potentially improve clinical outcomes in patients with acute brain injury by preventing such intracranial expansion. However, studies on the impact of TXA in these patients have yielded variable results, and its efficacy, appropriate dosing and optimal timing of administration remain unclear. The present review summarizes the clinical evidence regarding the proper use of tranexamic acid in the treatment of intracranial traumatic and non-traumatic hemorrhage, and its implications for clinical practice.

PALABRAS CLAVE
Ácido tranexámico;
Daño cerebral agudo;
Expansión del hematoma;
Traumatismo

Aplicaciones del ácido tranexámico en los pacientes neurocríticos: revisión narrativa

Resumen En los pacientes con hemorragia intracraneal, ya sea espontánea o traumática, la expansión del hematoma se asocia con peores resultados neurológicos y mayor mortalidad. La limitación del sangrado intracraneal y su expansión mediante la administración de un agente antifibrinolítico como el ácido tranexámico (ATX) puede mejorar potencialmente los desenlaces clínicos en pacientes con daño cerebral agudo. Sin embargo, los estudios sobre el impacto del

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craneoencefálico agudo;
Hemorragia subaracnoidea;
Hemorragia intracraneal

ATX en estos pacientes han mostrado resultados variables, y aún no está clara su eficacia, la dosificación adecuada y ni el momento óptimo de administración. El objetivo de esta revisión es resumir la evidencia clínica sobre el uso adecuado de ATX en el tratamiento de hemorragias intracraneales, tanto traumáticas como no traumáticas, y sus implicaciones para la práctica clínica.

Introduction

Tranexamic acid (TXA), a synthetic lysine analog, exhibits antifibrinolytic and anti-inflammatory properties, and has been shown to be effective in reducing the need for blood product transfusions in surgical patients,[1,2] preventing the progression of bleeding volume and controlling associated inflammation in trauma patients,[3,4] and reducing mortality in patients with perinatal hemorrhage.[5]

The use of TXA as an antifibrinolytic agent in patients with acute neurological structural disorders (traumatic brain injury [TBI], subarachnoid hemorrhage [SAH], or intracranial hemorrhage [ICH]), may help reduce or prevent the expansion of intracranial bleeding and the associated increased risk of death and disability. However, the role of TXA remains controversial,[6,7] and there is uncertainty regarding its clinical benefits, recommended dose, and associated risks.

The present narrative review summarizes the most relevant clinical evidence on the effects of TXA in neurocritical patients, and establishes recommendations for its use, based on the reviewed literature.

Methodology

Articles were selected from the PubMed, EMBASE, Science Direct, and Cochrane databases using the terms: ''tranexamic acid'', ''traumatic brain injury'', ''intracerebral hemorrhage'' and ''subarachnoid hemorrhage'', with the Boolean operator ''OR'' and ''AND''.

Impact of the use of TXA in patients with traumatic brain injury

The CRASH-2 trial,[4] which included 20,211 patients with trauma (intra- and extracranial) and major extracranial hemorrhage, was the first randomized controlled trial (RCT) to demonstrate that the early administration (within 3 hours after injury)[8] of TXA reduces mortality without increasing the risk of adverse events.

The 2016 European guidelines[9] recommend (grade 1A) the use of TXA in trauma patients with bleeding or at risk of significant bleeding, within the first three hours after trauma (grade 1B), and administration of the first dose preferably en route to the hospital (grade 2C).

Subsequently, a nested RCT was conducted within CRASH-2,[10] which included 270 trauma patients with or at risk for significant extracranial hemorrhage, presenting TBI defined by a Glasgow Coma Scale (GCS) score of $\leq$ 14 and a computed tomography (CT) scan compatible with TBI. In this subgroup, TXA administration was associated with a nonsignificant reduction in hematoma growth (adjusted difference −3.8 ml, 95% confidence interval [CI] −11.5 to 3.9) and in the development of new intracranial hemorrhages. The observed nonsignificant trend towards possible clinical benefits, in terms of lower mortality and functional dependence, warranted further clinical trials in this population.

The CRASH-3 trial[11] in turn included 12,737 patients with TBI and GCS $\leq$ 12 or intracranial hemorrhage on CT and no severe extracranial hemorrhage, who were randomized to TXA (n = 6406, 50.3%) or placebo (n = 6331, 49.7%). Among the 9,202 patients (72.2%) treated within three hours after injury, head injury-related mortality at 28 days was lower in the TXA group (18.5% vs. 19.8%; RR 0.94, 95% CI 0.86–1.02) and in patients with mild to moderate TBI (GCS 9–15) (RR 0.78, 95% CI 0.64–0.95), but not in patients with severe TBI (GCS 3–8) (RR 0.99, 95% CI 0.91–1.07). Early treatment (< 3 hours) was more effective than late treatment (> 3 hours) in patients with mild and moderate TBI (p = 0.005), but the time to treatment had no apparent effect in patients with severe TBI (p = 0.73). The risk of vascular occlusive events and seizures was similar in both groups. The CRASH-3 study suggests that the effectiveness of TXA in the management of TBI depends on the severity of the injury and the time of treatment initiation, but has several limitations. These include subjective inclusion criteria, changes in the primary objective of the study, and possible biases in the classification of the cause of death. Its external validity is moreover questionable due to the majority participation of low-income countries. In addition, the study lacks sufficient power to analyze subgroups and raises doubts about the biological plausibility of the results, as TXA appears to be effective only in mild to moderate TBI, but not in severe TBI.[7] The benefit of the use of TXA in patients with TBI could be due not only to its antifibrinolytic effect and the prevention of bleeding but also to its anti-inflammatory effects, protection of the endothelium and improvement of platelet function.[12]

Several systematic reviews and meta-analyses have examined the effects of TXA in patients with TBI,[13–21] and their results are summarized in Table 1. Reviews and meta-analyses that predate the publication of the CRASH-3 study[13–16] and which mostly included patients from the CRASH-2 study, concluded that TXA is effective in reducing

Table 1 Main meta-analyses evaluating the effect of TXA in patients with traumatic brain injury.

Author	Year	Included studies and sample size (no. patients TXA/placebo)	Mortality	Neurological outcomes	Hematoma expansion	Adverse events
Zehtabahi S[13] 2 RCT	2014	CRASH-2 Collaborators (2011)[10] (n = 133/137) Yutthakasemsunt S (2013) [1*] (n = 120/118)	RR 0.64 (95% CI 0.41–1.02) p = 0.77	Death, vegetative state, or total dependency RR 0.77 (95% CI 0.59–1.02) p = 0.76	RR 0.76 (95% CI 0.58–0.98) p = 0.45	
Ker K[14] 2 RCT	2015	CRASH-2 Collaborators (2011)[10] (n = 133/137) Yutthakasemsunt S (2013) [1*] (n = 120/120)	RR 0.63 (95% CI 0.4–0.99) p = 0.05	Death or disability RR 0.77 (95% CI 0.58–1.02) p = 0.06	RR 0.75 (95% CI 0.58–0.98) p = 0.03	AMI RR 0.51 (95% CI 0.09–2.73) p = 0.43 Stroke RR 0.34 (95% CI 0.01–8.35) p = 0.51 DVT RR 0.25 (95% CI 0.03–2.26) p = 0.22
Weng S[15] 5 RCT	2019	CRASH-2 Perel P (2012) [2*] (n = 133/137) Yutthakasemsunt S (2013) [1*] (n = 120/118) Jokar A (2017) [3*] (n = 40/40) Chakroun-Walha O (2018) [4*] (n = 96/84) Fakharian E (2018) [5*] (n = 74/75)	RR 0.83 (95% CI 0.60–1.16) p = 0.28	Favorable RR 1.07 (95% CI 0.96–1.13) p = 0.30	RR 0.77 (95% CI 0.61–0.98) p = 0.03	Thrombotic events RR 0.95 (95% CI 0.50–1.79) p = 0.87
Chen H[16] 6 RCT	2020	CRASH-2 Collaborators (2011)[10] (n = 133/137) Yutthakasemsunt S (2013) [1*] (n = 120/118) CRASH-2 Roberts I (2013)[8] (n = 10.093/10.114) Jokar A (2017) [3*] (n = 40/40) Chakroun-Walha O (2018) [4*] (n = 96/84) Fakharian E (2018) [5*] (n = 74/75)	RR 0.91 (95% CI 0.85–0.97) p = 0.004	Unfavorable RR 0.72 (95% CI 0.47–1.11) p = 0.14	RR 0.78 95% CI (0.61–0.99) p = 0.04	Pulmonary embolism RR 1.86 95% CI (0.42–8.29) p = 0.42
Yokobori S[17] 7 RCT	2020	CRASH-2 Collaborators (2011)[10] (n = 133/137) Yutthakasemsunt S (2013) [1*] (n = 120/118) Jokar A (2017) [3*] (n = 40/40) Chakroun-Walha O (2018) [4*] (n = 96/84) Fakharian E (2018) [5*] (n = 74/75) CRASH-3 (2019)[11] (n = 4.613/4.514) Ebrahimi P (2019) [6*] (n = 40/40)	RR 0.93 (95% CI 0.85–1.01) p = 0.09	Unfavorable RR 0.76 (95% CI 0.55–1.06) p = 0.60		Ischemic or thromboembolic complications RR 1.33 (95% CI 0.35–5.04) p = 0.68

Table 1 (*Continued*)

Author	Year	Included studies and sample size (no. patients TXA/placebo)	Mortality	Neurological outcomes	Hematoma expansion	Adverse events
July J[18]	2020	CRASH-2 Roberts I (2013)[8] (n = 10.060/10.067)		Unfavorable		Vascular occlusion
		Yutthakasemsunt S (2013) [1*] (n = 120/118)	RR 0.92		RR 0.79	events
7 RCT		Jokar A (2017) [3*] (n = 40/40)	(95% CI	RR 0.93	(95% CI	
		Chakroun-Walha O (2018) [4*] (n = 96/84)	0.88–0.97)	(95% CI	0.64–0.97)	RR 0.85
		Fakharian E (2018) [5*] (n = 74/75)	p = 0.002	0.72–1.21)	p = 0.03	(95% CI 0.71–1.02)
		CRASH-3 (2019)[11] (n = 4.613/4.514)		p = 0.59		p = 0.09
		Rowell SE (2019) [7*] (n = 312/309)				
Lawati K[19]	2021	CRASH-2 Perel P (2012) [2*] (n = 133/137)		GOS < 4 or		
		Yutthakasemsunt S (2013) [1*] (n = 120/118)	RR 0.95	GOS-E ≤ 4	RR 0.77	RR 0.97
9 RCT		Jokar A (2017) [3*] (n = 40/40)	(95% CI		(95% CI	(95% CI 0.85–1.11)
		Chakroun-Walha O (2018) [4*] (n = 96/84)	0.88–1.02)	RR 0.9	0.58–1.03)	
		Fakharian E (2018) [5*] (n = 78/78)	p = 0.18	(95% CI		
		CRASH-3 (2019)[11] (n = 6.406/6.331)		0.69–1.17)		
		Ebrahimi P (2019) [6*] (n = 40/40)		p = 0.45		
		Rowell SE (2020) [7*] (n = 657/309)				
		Mousavinejad M (2020) [8*] (n = 20/20)				
Huang H[20]	2022	CRASH-2 Perel P (2012) [2*] (n = 133/137)		GOS < 4		
		Yutthakasemsunt S (2013) [1*] (n = 120/118)	RR 0.99		SMD −0.35	RR 0.93
13 RCT		Jokar A (2017) [3*] (n = 40/40)	(95% CI	RR 0.96	(95% CI	(95% CI 0.76–1.14)
		Chakroun-Walha O (2018) [4*] (n = 96/84)	0.92–1.06)	(95% CI	−0.62–0.08)	p = 0.48
		Fakharian E (2018) [5*] (n = 78/78)	p = 0.73	0.82–1.11)	p = 0.01	
		CRASH-3 (2019)[11] (n = 6.406/6.331)		p = 0.57		
		Ebrahimi P (2019) [6*] (n = 40/40)				
		Rowell SE (2020) [7*] (n = 657/309)				
		Mousavinejad M (2020) [8*] (n = 20/20)				
		Mojallal F (2020) [9*] (n = 56/44)				
		Mahmood A (2021) [10*] (n = 884/883)				
		Bossers SM (2021) [11*] (n = 693/1.134)				
		van Wessem K (2021) [12*] (n = 120/114)				
Song JX[21]	2024	CRASH-2 Perel P (2012) [2*] (n = 133/137)				Pulmonary embolism
		Yutthakasemsunt S (2013) [1*] (n = 120/118)	RR 0.92		RR 0.78	
10 RCT		Jokar A (2017) [3*] (n = 40/40)	(95% CI		(95% CI	RR 1.33
		Chakroun-Walha O (2018) [4*] (n = 96/84)	0.85–1.00)		0.62–0.97)	(95% CI 0.56–3.15)
		Fakharian E (2018) [5*] (n = 78/78)	p = 0.05		p = 0.03	p = 0.52
		CRASH-3 (2019)[11] (n = 4.613/4.514)				
		Ebrahimi P (2019) [6*] (n = 40/40)				
		Rowell SE (2020) [7*] (n = 657/309)				
		Mousavinejad M (2020) [8*] (n = 20/20)				
		Safari H (2021) [13*] (n = 47/47)				

RCT: randomized clinical trial; RR: relative risk; CI: confidence interval; AMI: acute myocardial infarction; DVT: deep vein thrombosis; GOS: Glasgow Outcome Scale; GOS-E: Glasgow Outcome Scale Extended; SMD: standardized mean difference; *reference in Supplementary material.

the risk of hematoma expansion, reducing the mortality rate, and improving functional outcomes in patients with TBI, without increasing the incidence of thrombotic events. As of 2020, systematic reviews and meta-analyses[14–21] incorporate the results of the CRASH-3 study (the largest clinical trial in the context of TBI and with the greatest weight in published meta-analyses) and confirm the effects of TXA in reducing hematoma expansion and the absence of adverse events associated with administration of the drug, but the effects referred to mortality are heterogeneous. It is interesting to note that the reviews that demonstrate an effect upon mortality are those that include all patients in the CRASH-2 trial (not only patients with TBI), and so the conclusions cannot be attributed specifically to the TBI patient population.

The only guidelines published to date that mention the use of TXA in patients with TBI are those corresponding to the pre-hospital management of TBI in their third edition,[22] in which reference is made to two clinical trials.[23,24] In these studies, the out-of-hospital administration of TXA in patients with moderate or severe TBI did not provide any clinical benefit, and even increased mortality. Based on the results of these studies and the CRASH-3 trial, these guidelines do not recommend the use of TXA in the pre-hospital setting.

In conclusion, the early administration of TXA may offer modest benefits in patients with mild to moderate TBI, by decreasing the expansion of intracranial hemorrhage and reducing mortality to a modest degree, but it has shown no effect in severe cases. Although the associated risk of adverse events is low, given the lack of clear clinical benefit, the authors do not recommend its use in patients with severe TBI. Its use could only be considered in patients with mild or moderate TBI (GCS 9 - 15) and with evidence of intracranial bleeding on the initial CT scan.

Impact of the use of TXA in patients with aneurysmal subarachnoid hemorrhage

Subarachnoid hemorrhage due to intracranial aneurysm rupture (aSAH) accounts for approximately 5% of all strokes. A major cause of death and disability in aSAH is aneurysmal rebleeding, which occurs before aneurysm occlusion can be performed in 10–22% of all affected patients, with its highest incidence occurring in the first 24 hours and peaking in the first 6 hours after the initial event.[25] Up to 60% of the patients who suffer rebleeding die, and another 30% develop severe sequelae.[26] The most effective way to prevent rebleeding is the endovascular or surgical exclusion of the ruptured aneurysm from the circulation as early as possible, and ideally within the first 24 hours.[27] However, in daily clinical practice, treatment of the aneurysm is often postponed, either because of a delay in diagnosis or due to patient transfer to a tertiary treatment center.[28]

Early studies suggested that the administration of antifibrinolytic drugs prior to aneurysm occlusion could reduce the rebleeding rate, but without improving the functional outcomes, probably at the expense of an increased risk of delayed cerebral ischemia (DCI). However, these studies tested the use of the antifibrinolytic drug in prolonged treatments (at least 10 days), at high doses, and did not make widespread use of specific DCI prevention measures.[29]

Subsequently, the first RCT evaluating the early (within the first 48 hours from hospital admission), and short-term (within the first 72 hours) administration of TXA in 596 aSAH patients reported a decrease in the risk of rebleeding (2.4% versus 10.8%), without an increased risk of late ischemic events, and with a reduction in mortality attributable to rebleeding of 80% – though again without improvement of the functional outcomes.[30] The next update of the Cochrane review,[31] in which this study was included, concluded that the short-term treatment results are promising, but that further randomized trials are needed.

The next large RCT is the recently published ULTRA study.[32] This trial was designed to evaluate the effect of administering TXA as soon as possible after the diagnosis of aSAH (aSAH of perimesencephalic distribution or traumatic origin was excluded, but the identification of a vascular anomaly as the cause of aSAH was not required), and for a short period (until aneurysm occlusion or up to a maximum of 24 hours), in order to reduce the risk of DCI. This study included 955 patients (480 in the treatment group and 475 in the control group), most with Fisher Scale grade IV (66% and 64%, respectively). There were no significant differences in functional outcomes at 6 months (percentage of patients with a favorable modified Rankin Scale [mRS] score of 0 - 3, 60% vs. 64%; OR 0.87, 95%CI 0.67 - 1.13). However, in a secondary analysis, the excellent functional outcome (mRS 0–2) rate was lower in the TXA group (48% vs. 56%; OR 0.74, 95% CI 0.57–0.96). There was no difference in mortality or in the rebleeding rate before aneurysm treatment (10% vs. 14%; OR 0.71, 95% CI 0.48–1.04). Nevertheless, no increase in adverse events was identified with the use of TXA, documenting similar DCI (23% vs. 22%; OR 1.01, 95% CI 0.74–1.37) and thromboembolic complication rates (11% vs. 13%; OR 0.81, 95% CI 0.48–1.38) in both groups.

In the latest Cochrane review published in 2022,[33] only this last RCT[32] was added to those published in the preceding review.[31] The authors concluded that antifibrinolytic therapy, after the adoption of ischemia preventive measures and administered within the first 72 hours, reduces the risk of rebleeding (RR 0.65, 95% CI 0.47–0.91, p = 0.01; 11 trials, 2,717 participants; absolute risk reduction 7%, 95% CI 3–12%; moderate quality evidence), with no increase in the risk of DCI (RR 1.10, 95% CI 0.83–1.46, p = 0.49; 2 trials, 1,318 participants; high-quality evidence), but with no improvement in overall survival or in the chance of functional independence. These results are consistent with those reported by the different published systematic reviews and meta-analyses,[29,31,33–39] the results of which are summarized in Table 2, although the studies analyzed present great heterogeneity in doses, time of initiation and duration of treatment.[40]

In a *post hoc* analysis of the ULTRA study,[41] all 813 participants with a cerebral aneurysm confirmed on CT angiography and/or digital subtraction angiography were included. There were no differences in functional outcome (mRS 0–3, 58% in the TXA group and 60% in the control group, OR 0.92, 95% CI 0.69–1.24) or in any of the secondary outcomes: excellent clinical outcome (mRS 0–2, OR 0.76, 95% CI 0.57–1.03), and all-cause mortality at 30 days (OR 0.91, 95% CI 0.65–1.28) and at 6 months (OR 1.10, 95% CI 0.80–1.52). However, a decrease in rebleeding before aneurysm treatment was observed (11.2% vs. 16.1%; OR 0.66, 95% CI 0.44–0.99), again

Table 2 Main meta-analyses evaluating the effect of TXA in patients with subarachnoid hemorrhage.

Author	Year	Included studies and sample size (no. patients TXA/placebo)	Mortality	Neurological outcomes	Rebleeding	Adverse events
Roos YB[29] 9 RCT	2003	Girvin JP (1973) [14*] (n = 39/27) Van Rossum J (1977) [15*] (n = 26/25) Chandra B (1978) [16*] (n = 20/19) Maurice-Williams RS [17*] (1978) (n = 25/25) Kaste M (1979) [18*] (n = 32/32) Fodstad H (1981) [19*] (n = 30/29) Vermeulen M (1984) [20*] (n = 241/238) Tsementzis SA (1990) [21*] (n = 50/50) Roos Y (2000) [22*] (n = 229/233)	OR 0.99 (95% CI 0.79–1.24) p = 0.23	Death, vegetative state, severe disability OR 1.12 (95% CI 0.88–1.43) p = 0.75	OR 0.45 (95% CI 0.32–0.61) p < 0.0001	DCI OR 1.34 (95% CI 0.98–1.82) p = 0.07 Hydrocephalus OR 1.24 (95% CI 0.86–1.85) p = 0.3
Baharoglu MI[31] 10 RCT	2013	Girvin JP (1973) [14*] (n = 39/27) Van Rossum J (1977) [15*] (n = 26/25) Chandra B (1978) [16*] (n = 20/19) Maurice-Williams RS (1978) [17*] (n = 25/25) Kaste M (1979) [18*] (n = 32/32) Fodstad H (1981) [19*] (n = 30/29) Vermeulen M (1984) [20*] (n = 241/238) Tsementzis SA (1990) [21*] (n = 50/50) Roos Y (2000) [22*] (n = 229/233) Hillman J (2002)[30] (n = 254/251)	OR 1 (95% CI 0.85–1.18) p = 0.98	Death, vegetative state, severe disability OR 1.02 (95% CI 0.91–1.15) p = 0.71	OR 0.44 (95% CI 0.26–0.75) p = 0.002	DCI OR 1.34 (95% CI 0.88–2.03) p = 0.17 Hydrocephalus OR 1.17 (95% CI 0.87–1.55) p = 0.03
Feng Y[34] 4 RCT 1 Observational	2021	Fodstad H (1981) [19*] (n = 30/29) Vermeulen M (1984) [20*] (n = 241/238) Wijdicks EF (1989) [23*] (n = 119/238) Post R (2019) [24*] (n = 119/390) Post R (2021)[32] (n = 480/475)	OR 0.94 (95% CI 0.75–1.18) p = 0.61	Unfavorable OR 0.95 (95% CI 0.61–1.48) p = 0.82	OR 0.62 (95% CI 0.41–0.93) p = 0.02	DCI OR 1.34 (95% CI 0.78–2.04) p = 0.34 Hydrocephalus 1.17 (95% CI 0.94–1.46) p = 0.17
Liu L[35] 7 RCT	2021	Fodstad H (1981) [19*] (n = 30/29) Vermeulen M (1984) [20*] (n = 241/238) Wijdicks EF (1989) [23*] (n = 119/238) Tsementzis SA (1990) [21*] (n = 50/50) Roos Y (2000) [22*] (n = 229/233) Hillman J (2002)[30] (n = 254/251) Post R (2021)[32] (n = 480/475)	DR 0.00 (95% CI −0.00–0.04) p = 0.91	Favorable (GOS $\geq$ 4) DR −0.01 (95% CI −0.05–0.02) p = 0.51	DR −0.06 (95% CI −0.09 to −0.03) p = 0.000	DCI DR 0.00 (95% CI −0.03–0.03) p = 0.96 Hydrocephalus DR 0.04 (95% CI 0.01–0.08) p = 0.02

Table 2 (*Continued*)

Author	Year	Included studies and sample size (no. patients TXA/placebo)	Mortality	Neurological outcomes	Rebleeding	Adverse events
Ren J[36] 10 RCT	2022	van Rossum J (1977) [15*] (n = 26/25) Chandra B (1978) [16*] (n = 20/19) Maurice-Williams RS (1978) [17*] (n = 25/25) Kaste M (1979) [18*] (n = 32/32) Fodstad H (1980) [25*] (n = 53/52) Vermeulen M (1984) [20*] (n = 241/238) Tsementzis SA (1990) [21*] (n = 50/50) Roos Y (2000) [22*] (n = 229/233) Hillman J (2002)[30] (n = 254/251) Post R (2021)[32] (n = 480/475)	RR 1.00 (95% CI 0.81–1.22) p = 0.97	Favorable (mRS < 3) RR 0.99 (95% CI 0.88–1.11) p = 0.86	RR 0.53 (95% CI 0.39–0.71) p < 0.0001	DCI RR 1.18 (95% CI 0.89–1.56) p = 0.24 Hydrocephalus RR 1.13 (95% CI 1.02–1.24) p = 0.01
Ghaith HS[37] 13 RCT	2022	Van Rossum J (1977) [15*] (n = 26/25) Chandra B (1978) [16*] (n = 20/19) Maurice-Williams RS (1978) [17*] (n = 25/25) Kaste M (1979) [18*] (n = 32/32) Gelmers HJ (1980) [26*] (n = 26/31) Fodstad H (1981) [19*] (n = 30/29) Fodstad H (1981) [27*] (n = 21/20) Vermeulen M (1984) [20*] (n = 241/238) Tsementzis SA (1990) [21*] (n = 50/50) Roos Y (2000) [22*] (n = 229/233) Hillman J. (2002)[30] (n = 254/251) Post R (2021)[32] (n = 480/475)	RR 1.00 (95% CI 0.81–1.24) p = 0.97	Favorable (mRS 0–3 or GOS = 1) RR 0.98 (95% CI 0.91–1.06) p = 0.69	RR 0.56 (95% CI 0.44–0.72] p < 0.00001	DCI RR 1.22 (95% CI 0.89–1.66) p = 0.22 Hydrocephalus RR 1.1 (95% CI 1–1.21) p = 0.05
Shi M[38] 13 RCT	2022	Gibbs JR (1971) [28*] (n = 22/25) Van Rossum J (1977) [15*] (n = 26/25) Chandra B (1978) [16*] (n = 20/19) Maurice-Williams RS [17*] (1978) (n = 25/25) Fodstad H (1978) [29*] (n = 23/23) Kaste M (1979) [18*] (n = 32/32) Fodstad H (1981) [19*] (n = 30/29) Fodstad H (1981) [27*] (n = 21/20) Vermeulen M (1984) [20*] (n = 241/238) Tsementzis SA (1990) [21*] (n = 50/50) Roos Y (2000) [22*](n = 229/233) Hillman J (2002)[30] (n = 254/251) Post R (2021)[32] (n = 480/475)	RR 0.96 (95% CI 0.84–1.10) p = 0.55	Unfavorable (mRS $\geq$ 4 or GOS $\leq$ 3) RR 1.04 (95% CI 0.95–1.15) p = 0.41	RR 0.59 (95% CI 0.43–0.82) p = 0.001	DCI RR 1.17 (95% CI 0.95–1.46) p = 0.15 Hydrocephalus RR 1.09 (95% CI 0.99–1.2) p = 0.10

Table 2 (*Continued*)

Author	Year	Included studies and sample size (no. patients TXA/placebo)	Mortality	Neurological outcomes	Rebleeding	Adverse events
Germans MR[33] 11 RCT	2022	Girvin JP (1973) [14*] (n = 39/27) Van Rossum J (1977) [15*] (n = 26/25) Chandra B (1978) [16*] (n = 20/19) Maurice-Williams RS (1978) [17*] (n = 25/25) Kaste M (1979) [18*] (n = 32/32) Fodstad H (1981) [19*] (n = 30/29) Vermeulen M (1984) [20*](n = 241/238) Tsementzis SA (1990) [21*] (n = 50/50) Roos Y (2000) [22*] (n = 229/233) Hillman J (2002)[30] (n = 254/251) Post R (2021)[32] (n = 480/475)	RR 1.02 (95% CI 0.90–1.16) p = 0.77	Death, vegetative state, severe disability RR 1.03 (95% CI 0.94–1.13) p = 0.53	RR 0.65 (95% CI 0.47–0.91) p = 0.01	DCI RR 1.17 (95% CI 0.9–1.51) p = 0.25 Hydrocephalus RR 1.09 (95% CI 0.99–1.21) p = 0.09
Fatima K[39] 11 RCT 1 Observational	2023	Van Rossum J (1977) [15*] (n = 26/25) Chandra B (1978) [16*] (n = 20/19) Maurice-Williams RS (1978) [17*] (n = 25/25) Kaste M (1979) [18*] (n = 3 2/32) Gelmers HJ (1980) [26*] (n = 26/31) Fodstad H (1981) [19*] (n = 30/29) Vermeulen M (1984) [20*] (n = 241/238) Tsementzis SA (1990) [21*] (n = 50/50) Roos Y (2000) [22*] (n = 229/233) Hillman J (2002)[30] (n = 254/251) Post R (2019) [24*] (n = 119/390) Post R (2021)[32] (n = 480/475)	OR 0.92 (95% CI 0.72–1.45) p = 0.5	Death, vegetative state, severe disability (mRS $\geq$ 4 or GOS $\leq$ 3) OR 1.02 (95% CI 0.86–1.2) p = 0.85	OR 0.55 (95% CI 0.4–0.75) p = 0.0002	DCI OR 1.19 (95% CI 0.88–1.6) p = 0.26

RCT: randomized clinical trial; RR: relative risk; CI: confidence interval; DR: difference of risks; OR: odds ratio; GOS: Glasgow Outcome Scale; mRS: modified Rankin Scale; DCI: delayed cerebral ischemia; *: reference in Supplementary material.

with no increase in the incidence of DCI (OR 0.99, 95% CI 0.72–1.36).

A new *post hoc* analysis of the ULTRA study[42] investigated the impact of time to initiation of TXA on rebleeding and functional outcome after aSAH. It included 807 patients stratified into three categories according to the time of treatment initiation (0–3, 3–6, and more than 6 hours). Patients in the TXA group had fewer rebleeding episodes (16.2% vs. 19.9%; HR 0.86, 95% CI 0.62–1.19), and the time of initiation of TXA was found to have a significant effect on the rebleeding rate ($p < 0.001$). However, a protective effect was only observed when TXA was initiated after 6 hours (absolute rate reduction of 1.4%). This effect was not clinically relevant, given the low number of rebleeding episodes in this time window, with a minimal overall impact on the total rebleeding rate. Treatment with TXA showed no effect in terms of obtaining a favorable functional outcome (OR 0.96, 95% CI 0.72–1.27), with no evidence of effect modification according to the time of TXA initiation ($p = 0.53$).

The 2023 American guidelines of the AHA/ASA,[43] which refer to the ULTRA study, have recently been published. These guidelines do not recommend the routine use of TXA in patients with aSAH (class 3 recommendation, level of evidence A), due to the variability of the results in the published trials. However, they do consider the possibility of its use with a short duration in patients whose aneurysm treatment is delayed due to logistical or medical circumstances.

In sum, the administration of TXA in patients with aSAH prior to aneurysm occlusion can reduce the risk of rebleeding, without an increase in adverse events, but without improvement in the functional outcomes or a decrease in mortality. Therefore, the authors consider that antifibrinolytic agents should not be used routinely, but may be a therapeutic option when used for a short period of time (< 72 hours) to reduce the risk of rebleeding, in patients with an unavoidable delay of aneurysm occlusion (> 24 hours), and without medical contraindications such as risk factors for the development of thromboembolic complications (previous history of thromboembolic disease or hypercoagulability, acute ECG alterations, troponin elevation, or symptoms of thromboembolism) and/or severe renal failure (creatinine > 1.7 mg/dl). TXA administration should be discontinued 2–4 hours before the endovascular procedure, since arteriography itself carries a thromboembolic risk.

Impact of the use of TXA in patients with spontaneous intracranial hemorrhage

Although non-traumatic or spontaneous intracranial hemorrhage (ICH) accounts for only 10–20% of all strokes, it is responsible for nearly half of all stroke deaths, and is associated with significant morbidity.[44] Hematoma expansion (HE) (defined as an increase of $\geq$ 6 ml or 33% of the baseline hematoma) occurs in up to one-third of the patients after ICH, and is the leading cause of neurological deterioration. In almost half of the patients, HE occurs within 24 hours of symptoms onset, being more frequent in the first 4–6 hours, and is associated with a poorer prognosis, greater functional disability, and higher mortality.[45]

The first study to analyze the use of TXA in spontaneous ICH was the TICH-2 trial.[46] This was a RCT comparing TXA treatment vs. placebo, in which 2,325 patients from 12 countries were included. TXA administration produced a significant but modest reduction in HE (OR 0.80, 95% CI 0.66–0.8, $p = 0.03$) and early 7-day mortality (OR 0.73, 95% CI 0.53–0.99, $p = 0.04$), but with no significant difference in functional outcome or 90-day mortality. However, a subgroup of patients with a baseline systolic blood pressure (SBP) of $\leq$ 170 mmHg was identified in whom TXA administration was associated with improvement of the modified Rankin Scale (mRS) score at 90 days (OR 0.73, 95% CI 0.59–0.9). This result may be confounded by the effect of ICH severity, since larger volume hematomas are accompanied by higher SBP values and poorer outcomes.[47] The use of TXA was not associated with an increase in thromboembolic events or other serious adverse events. One of the limitations of this study was due to the heterogeneity of the included population, involving a large proportion of patients with intraventricular hemorrhage (32%). The lack of benefit of TXA could be due to the fact that most patients were treated more than three hours after the onset of the hemorrhage, outside the ideal window to prevent HE. On the other hand, given that functional recovery from ICH can take several months (up to 6 months), it might have been necessary to extend the follow-up time.[48]

A subsequent clinical trial (TICH-NOAC)[49] involving a small sample size included 63 patients with ICH receiving non-vitamin K antagonist oral anticoagulants. In this study, the incidence of HE (38% vs. 45%, aOR 0.63, 95% CI 0.22–1.82, $p = 0.40$), mortality (47% vs. 42%, aOR 1.07, 95% CI 0.37–3.04, $p = 0.91$) and thromboembolic complications (13% vs. 6%, aOR 1.86, 95% CI 0.37–9.50, $p = 0.45$) did not differ between the TXA-treated group and the placebo group. However, this trial was terminated prematurely due to the exhaustion of funds.

Following the TICH-2 study, special emphasis has been placed on identifying patients at higher risk for HE and, therefore, with greater potential benefit from the use of TXA. The spot sign on CT angiography or contrast-enhanced CT, indicating contrast extravasation and active leakage of blood in the hematoma area, is a predictor of HE. However, recent studies such as the STOP-AUST, published in 2020,[50] and two others published in 2021 - an analysis of a pre-specified subgroup of the TICH-2 trial[51] and the TRAIGE study[52] - found no significant benefit of TXA in patients with spot sign in terms of HE, functional outcomes, mortality, or thromboembolic events. Although a slight trend towards lower mortality was observed in the TRAIGE study,[52] the results were inconclusive due to limitations such as a small sample size, probably related to the difficulty of performing imaging tests with optimal timing, as well as correct identification of the spot sign,[53] and delays in treatment. The results of these studies are summarized in Table 3.

Overall, the main meta-analyses and systematic reviews on the use of TXA in patients with spontaneous ICH[54–60] - the results of which are listed in Table 4 - conclude that TXA reduces HE, but without significant benefits in functional outcome or patient mortality.

Finally, the results of the STOP-MSU study have recently been published.[61] This is an RCT involving 202 patients, carried out to determine the effect of treatment with TXA in

Table 3 Main randomized clinical trials evaluating the effect of TXA in patients with spontaneous intracranial hemorrhage and identification of the spot sign.

Author	Year	Included studies and sample size (no. patients TXA/placebo)	Mortality	Neurological outcomes	Hematoma expansion	Thromboembolic events
Meretoja A[50] STOP-AUST	2020	100 (50/50)	26% vs 16% OR 2.38 (95% CI 0.66–8.67) p = 0.19	Unfavorable (mRS 4–6) OR 1.0 (95% CI 0.63–1.61) p = 0.97	44% vs 52% OR 0.72 (95% CI 0.32–1.59) p = 0.41	2% vs 4% OR 0.49 (95% CI 0.04–5.58) p = 0.57
Ovensen C[51] Subgroup of TICH-2	2021	254 With ''spot sign'': (30/34) Without ''spot sign'': (95/95)	With ''spot sign'': HR 1.50 (95% CI 0.62–3.67) Without ''spot sign'': HR 0.75 (95% CI 0.36–1.55)	With ''spot sign'': OR 0.72 (95% CI 0.21–2.55) Without ''spot sign'': OR 1.18 (95% CI 0.60–2.32)	With ''spot sign'': aOR 0.85 (95% CI 0.29–2.46) Without ''spot sign'': aOR 0.77 (95% CI 0.41–1.45)	With ''spot sign'': OR 1.15 (95% CI 0.21–6.17) Without ''spot sign'': OR 0.65 (95% CI 0.18–2.39)
Liu J[52] TRAIGE	2021	171 (36/34)	8.1% vs 10.0% OR 0.82 (95% CI 0.28–2.37) p = 0.71	Unfavorable (mRS 4–6) OR 1.23 (95% CI 0.65–2.33) p = 0.53	40.4% vs 41.5% OR 0.96 (95% CI 0.52–1.77) p = 0.89	1.2% vs 1.3% p = 0.96

OR: odds ratio; CI: confidence interval; HR: hazard ratio; mRS: modified Rankin scale; aOR: adjusted odds ratio.

Table 4 Main meta-analyses evaluating the effect of TXA in patients with spontaneous intracranial hemorrhage.

Author	Year	Included studies and sample size (no. patients TXA/placebo)	Mortality	Neurological outcomes	Hematoma expansion	Adverse events
Wang X[54] 6 RCT	2021	Sprigg N (TICH-1) (2014) [30*] (n = 16/8) Arumugam A (2015) [31*] (n = 15/15) Sprigg n (TICH-2) (2018)[46] (n = 1161/1164) Meretoja A (2020)[50] (n = 50/50) Ni J (2020) [32*] (n = 13/77) Liu J (TRAIGE) (2021)[52] (n = 89/82)	RR 1.01 (95% CI 0.87–1.18) p = 0.86	Favorable (mRS $\leq$ 2) RR 1.10 (95% CI 0.92–1.32) p = 0.27	RR 0.87 (95% CI 0.77–0.99) p = 0.03	Thromboembolic events RR 1.20 (95% CI 0.85–1.69) p = 0.30
Guo Y[55] 5 RCT 1 post-hoc analysis 1 subgroups analysis	2021	Sprigg N (TICH-1)(2014) [30*] (n = 16/8) Arumugam A (2015) [31*] (n = 15/15) Sprigg N (TICH-2) (2018)[46] (n = 1161/1164) Meretoja A (STOP-AUST) (2020)[50] (n = 50/50) Law ZK. Post-hoc TICH – 2 (2020) [33*] (n = 2325) Ovesen C. Subgroups TICH-2 (2021)[51] (n = ''spot sign'' positive: 27/30 and ''spot sign'' negative: 80/78) Liu J (2021)[52] (n = 89/82)	OR 1.02 (95% CI 0.84–1.23) p = 0.83	Unfavorable (death or disability) (mRS 4–6) OR 0.99 (95% CI 0.84–1.15) p = 0.91	OR 0.82 (95% CI 0.69–0.98) p = 0.03	Major thromboembolic events OR 1.09 (95% CI 0.72–1.65) P = 0.67
Bouillon-Minois JB[56] 3 RCT (HIC)	2021	Sprigg N (TICH-1) (2014) [30*] (n = 16/8) Sprigg N (TICH-2) (2018)[46] (n = 1161/1164) Meretoja A (STOP-AUST) (2020)[50] (n = 50/50)	RR 1.02 (95% CI 0.86–1.17) NS	-	-	-
Gao B[57] 3 RCT	2021	Sprigg N (TICH-1) (2014) [30*] (n = 16/8) Arumugam A (2015) [31*] (n = 15/15) Sprigg N (TICH-2) (2018)[46] (n = 1161/1164)	-	-	RR 0.84 (95% CI 0.74–0.97) p = 0.02	-

Table 4 (*Continued*)

Author	Year	Included studies and sample size (no. patients TXA/placebo)	Mortality	Neurological outcomes	Hematoma expansion	Adverse events
Yu Z[58] 3 RCT 1 observational study	2023	Sorimachi T (2007) [34*] (n = 188) Sprigg N (TICH-1) (2014) [30*] (n = 16/8) Arumugam A (2015) [31*] (n = 15/15) Sprigg N (TICH-2) (2018)[46] (n = 1161/1164)	OR 1.14 (95% CI 0.73–1.77) p = 0.58	Favorable (mRS 0–3) OR 1.06 (95% CI 0.89–1.26) p = 0.51	OR 0.81 (95% CI 0.68–0.97) p = 0.02	Major thromboembolic events OR 1.04 (95% CI 0.67–1.62) p = 0.87
Xiong Y[59] 5 RCT	2023	Sprigg N (TICH-1) (2014) [30*] (n = 16/8) Arumugam A (2015) [31*] (n = 15/15) Sprigg N (TICH-2) (2018)[46] (n = 1161/1164) Meretoja A (STOP-AUST) (2020)[50] (n = 50/50) Liu J (TRAIGE) (2021)[52] (n = 89/82)	OR 1.02 (95% CI 0.84–1.23) p = 0.84	Favorable (mRS $\leq$ 2) OR 1.05 (95% CI 0.89–1.24) p = 0.58	MD −1.78 (95% CI −2.78 to −0.79) p < 0.001	-
Eilertsen H[60] 5 RCT	2023	Sprigg N (TICH-1) (2014) [30*] (n = 16/8) Sprigg N (TICH-2) (2018)[46] (n = 1161/1164) Meretoja A (STOP-AUST) (2020)[50] (n = 50/50) Liu J (TRAIGE) (2021)[52] (n = 89/82) Polymeris AA (TICH-NOAC) (2023)[49] (n = 32/31)		Unfavorable (death or dependency) (mRS 4–6) RR 1.00 (95% CI 0.93–1.07) p = 0.99	RR 0.86 (95% CI 0.76–0.96) p = 0.008	Thromboembolic events RR 1.23 (95% CI 0.88–1.71) p = 0.23

RCT: randomized clinical trial; RR: relative risk; CI: confidence interval; mRS: modified Rankin scale; OR: odds ratio; MD: mean difference; *reference in Supplementary material.

the two hours following ICH. No differences were observed compared to placebo in any of the following outcomes: HE at 24 hours (43% vs. 38%, OR 1.31, 95% CI 0.72–2.40, p = 0.37), functional outcome at day 90 (OR 0.83, 95% CI 0.60–1.14), 7-day mortality (8% vs. 8%, OR 1.08, 95% CI 0.35–3.35), or 90-day mortality (18% vs. 15%, OR 1.61, 95% CI 0.65–3.98); likewise, no significant differences were observed in the subgroup analysis either. Factors that may have contributed to these findings include the enrollment of patients with relatively small and deep hematomas, and the small mean absolute growth of the basal hematomas at 24 hours. The limitations of this study include a small sample size, and the fact that only the initial patient SBP was recorded, so that the possible interaction between the effect of TXA and SBP control in HE could not be studied.

The latest AHA/ASA guidelines[62] do not establish any recommendation for the use of TXA in patients with ICH, and state with a level of evidence 2b that in patients with spontaneous ICH (with or without the spot sign), the efficacy of TXA in improving the functional outcome is not well established.

In conclusion, the use of TXA does not improve the functional outcomes or influence patient mortality in spontaneous ICH, and has only demonstrated small reductions in hematoma volume, which do not justify its use. New studies are needed, without the limitations of the previous ones, involving an adequate sample size, the inclusion of patients with radiological signs of high risk of HE, longer follow-up times, early administration of TXA, and evaluation of the concomitant effect of close monitoring and management of SBP.

Currently, investigators in the TICH study are conducting a large phase 3 trial, involving 5,500 participants, of TXA vs. placebo, to be administered within 4.5 hours after symptoms onset - the primary objective being to assess 7-day mortality.[63]

Thus, based on the currently available evidence and pending the results of new studies, the authors do not recommend the administration of TXA in patients with spontaneous ICH.

Conclusions

Based on the published studies, while TXA offers a modest benefit in terms of mortality in patients with mild or moderate TBI, its use is discouraged in severe cases and can only be generally recommended in the presence of extracranial lesions. In patients with aSAH, the prevention of rebleeding should focus on early endovascular or surgical obliteration of the aneurysm causing the initial bleeding; however, TXA may have a role in situations where rapid intervention is not possible. And, in patients with non-traumatic ICH, data have shown only small decreases in hematoma volume. Therefore, despite the absence of adverse events, TXA does not improve the functional outcomes or influence mortality, so its use cannot be routinely recommended. Further studies are needed to establish which type of patients with acute brain injury are most likely to benefit from TXA, along with the optimal dose and timing of administration.

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Declaration of competing interest

The authors declare that they have no conflicts of interest. No permission from any institution is required for publication of this manuscript.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.medine.2025.502139.

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