



Clinical Outcomes of Tranexamic Acid in Acute Traumatic Brain Injury: Systematic Review and Meta-Analysis

¹Dr. Manish Kokne, ²Dr. Prasad Pandit, ³Dr. Kiran Bhawe, ⁴Dr. Tejal Patel and ⁵Dr. Pratiksha Kapse

¹Associate Professor, ESIC Medical College, Andheri, Mumbai, Maharashtra, India

²Professor, HBTMC & Dr RN Cooper Hospital, Vile Parle, Mumbai, Maharashtra, India

³Professor, HBTMC & Dr RN Cooper Hospital, Vile Parle, Mumbai, Maharashtra, India

⁴Additional Professor, HBTMC & Dr RN Cooper Hospital, Vile Parle, Mumbai, Maharashtra, India

⁵Assistant Professor, HBTMC & Dr RN Cooper Hospital, Vile Parle, Mumbai, Maharashtra, India

Corresponding Author: Dr. Manish Kokne

Abstract:

Background: Traumatic brain injury (TBI) complicated by intracranial hemorrhage is a major contributor to morbidity and mortality among trauma patients. Tranexamic acid, an antifibrinolytic agent widely used to reduce surgical blood loss, has been proposed as a potential intervention to limit hemorrhage progression and improve clinical outcomes in patients with acute TBI.

Objective: To evaluate the efficacy and safety of tranexamic acid in patients with acute traumatic brain injury.

Methods: A systematic review of randomized controlled trials was conducted. An advanced search of PubMed was performed in August 2025, supplemented by searches of the Cochrane Collaboration database, Google Scholar®, and clinical trial registries. Eligible studies included prospective randomized controlled trials evaluating tranexamic acid in patients with traumatic brain injury. Data were independently extracted from included studies. Outcomes assessed included mortality, adverse events, requirement for neurosurgical intervention or blood transfusion, volume of blood transfused, intracranial hemorrhage growth and expansion, ischemic brain lesions, and functional disability at discharge. The quality of evidence was assessed using the GRADE approach.

Results: Five randomized controlled trials met the inclusion criteria, comprising a total of 13477 patients. The pooled analysis demonstrated that tranexamic acid significantly reduced the risk of intracranial hemorrhage growth by 52% (RR 0.48, 95% CI 0.61–0.98; $p = 0.03$). Tranexamic acid also significantly reduced the risk of unfavorable functional status at discharge by 24% (RR 0.76, 95% CI 0.61–0.93; $p = 0.009$). No significant effect of tranexamic acid was observed on mortality, need for neurosurgical intervention, or total hemorrhage expansion. No increase in risk of adverse events was reported.

Conclusion: Tranexamic acid administered within eight hours of injury safely reduces intracranial hemorrhage progression and unfavorable functional outcomes at discharge, thereby limiting morbidity in patients with traumatic brain injury without increasing the risk of adverse events. While these findings suggest a beneficial role for Tranexamic Acid in reducing morbidity, uncertainty regarding its impact on mortality remains, highlighting the need for further well-designed randomized trials

Keywords: Traumatic brain injury, Tranexamic acid, Intracranial hemorrhage, Functional outcome

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Introduction

Laparoscopic cholecystectomy (LC) has become the gold standard for treating Traumatic brain injury (TBI) is a physical injury to brain tissue that results in temporary or permanent impairment of brain function. The diagnosis of

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TBI is suspected clinically and confirmed by neuroimaging modalities such as computed tomography (CT) or magnetic resonance imaging (MRI). Initial management focuses on securing a reliable airway, maintaining adequate ventilation, and ensuring optimal blood pressure to preserve cerebral



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perfusion. In more severe cases, surgical intervention may be required to evacuate intracranial hematomas or to relieve raised intracranial pressure (ICP). During the early post-injury period, intensive efforts are directed toward maintaining cerebral perfusion and oxygenation while preventing secondary complications that may lead to altered sensorium. Many patients subsequently require prolonged periods of rehabilitation [1, 2].

TBI represents a major global public health burden and is a leading cause of death and disability worldwide. The rising incidence of TBI reflects, in part, the increasing rates of road traffic accidents and trauma-related violence, particularly in low- and middle-income countries, where approximately 90% of all TBI-related deaths occur [3]. Globally, the incidence of TBI is estimated to range between 200 and 600 injuries per 100,000 population per year [4]. TBI accounts for approximately 1.4 million emergency department visits and 52,000 deaths annually, with an estimated economic burden of nearly 60 billion US dollars [5, 6]. In the United Kingdom, nearly one million individuals attend emergency departments each year with TBI [7]. According to the World Health Organization, road traffic accidents are the leading cause of injury-related deaths worldwide, claiming nearly 1.3 million lives annually [8]. Falls are the second most common cause of TBI-related mortality, accounting for over 600,000 deaths globally [9]. In older adults, falls account for nearly 80% of TBI-related emergency visits, hospitalizations, and deaths [10, 11]. Violence-related TBI, whether self-inflicted or interpersonal, also contributes significantly, particularly in the United States, where firearm-related deaths rival those caused by road traffic accidents [10].

The pathophysiology of TBI involves both primary and secondary brain injury mechanisms. Primary injury results from direct mechanical damage such as contusion, laceration, or crushing of brain tissue [12]. TBI of any severity can lead to cerebral edema, resulting in increased ICP. Cerebral blood flow is dependent on cerebral perfusion pressure (CPP), defined as the difference between mean arterial pressure (MAP) and ICP. As ICP rises or MAP falls, CPP decreases, and when CPP drops below approximately 50 mm Hg, cerebral ischemia may ensue [13]. Ischemia and edema trigger a cascade of secondary injury mechanisms, including excitatory neurotransmitter release, free radical production, cytokine-mediated inflammation, and cell membrane damage, further worsening cerebral edema and ICP [12, 14, 15]. Systemic insults such as hypotension and hypoxia further exacerbate secondary brain injury. Uncontrolled ICP elevation may result in cerebral herniation, significantly increasing morbidity and mortality. In extreme cases, ICP equal to MAP leads to cessation of cerebral perfusion, resulting in brain death [16, 17].

Clinically, patients with significant TBI often experience an initial loss of consciousness, confusion, or amnesia. Seizures may occur early, particularly within the first 24 hours. The Glasgow Coma Scale (GCS) provides a rapid and reproducible assessment of injury severity during initial evaluation. [18] Lower GCS scores correlate with worse outcomes and higher mortality [19, 21]. Although GCS is widely used to classify TBI severity, prognosis is more accurately determined when combined with CT findings and clinical features.

Progressive intracranial hemorrhage and cerebral edema leading to ischemia are major contributors to poor outcomes following TBI [22-25]. These processes are further aggravated

by post-traumatic coagulopathy, which is present in approximately one-third of patients and is associated with elevated fibrin degradation products within the first three hours following injury [26, 27]. Patients with coagulopathy have a significantly increased risk of intracranial hemorrhage progression and up to a ten-fold increase in mortality [23, 28, 29]. Tranexamic acid is an antifibrinolytic agent that reduces bleeding by inhibiting fibrin clot degradation. Tranexamic acid is administered as a 1 g intravenous loading dose over 10 minutes, followed by a maintenance infusion of 1 g intravenously over 8 hours, resulting in a total dose of 2 g. It is widely used in trauma and surgical settings and has been shown to reduce blood loss and transfusion requirements in patients undergoing surgery [30, 31]. In trauma patients with extracranial hemorrhage, early administration of Tranexamic acid significantly reduces death due to bleeding when administered within the first three hours of injury [32, 33]. Beyond this window, the benefit diminishes and may even be harmful [33]. Given that intracranial bleeding is most active in the early post-injury period, Tranexamic acid may be most effective when administered soon after TBI [34].

However, concerns regarding the safety of Tranexamic Acid in TBI remain. By inhibiting fibrinolysis, Tranexamic Acid may theoretically increase the risk of cerebral ischemia or thrombosis, which are already recognized complications of TBI [35, 37]. Additionally, Tranexamic Acid crosses the blood-brain barrier and has been associated with seizures, raising concerns in patients with disrupted blood-brain barrier following TBI [38, 39]. Despite these concerns, the mechanistic potential of Tranexamic Acid to reduce secondary brain injury has generated interest in its role as a therapeutic intervention in TBI.

Given the biological plausibility, high disease burden, and conflicting evidence from individual trials, a systematic analysis of available randomized controlled trials is warranted. This systematic review and meta-analysis were therefore undertaken to evaluate the clinical outcomes of tranexamic acid administration in patients with acute TBI, focusing on mortality, neurological function, hemorrhage progression, and safety outcomes.

Materials and Methods

Literature Search

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [40]. A pre-designed protocol guided the literature search, trial selection, data extraction, and quality assessment. An advanced search of PubMed was performed in August 2025, supplemented by searches of the Cochrane Collaboration database, Google Scholar®, and clinical trial registries.

A comprehensive electronic search was performed in PubMed/MEDLINE, Cochrane Central Register of Controlled Trials, Google Scholar®, and relevant clinical trial registries using combinations of search terms including “*tranexamic acid*”, “*extracranial trauma*”, “*TBI*”, “*TBI*”, “*intracranial hemorrhage*”, and “*randomized controlled trial*”. Searches were limited to clinical trials and human studies. Reference lists of relevant articles and previous reviews were also screened to identify additional trials.

Initial PubMed search with “*tranexamic acid AND trauma*” yielded 55 articles, and the Cochrane database search returned 9 articles. From these and additional searches, 6



primary trials were identified that directly examined the effect of tranexamic acid in patients with TBI.

Inclusion and Exclusion Criteria

Participants: Emergency department patients with TBI (TBI) or at risk of intracranial hemorrhage (ICH) following trauma. TBI definitions varied, but were accepted as used by the original trials.

- **Intervention:** Intravenous tranexamic acid administered at any dose, timing, or route post-TBI.
- **Control:** Matching placebo

Outcomes

- **Primary:** Mortality from any cause within the follow-up period of each trial; neurological outcomes (e.g., Glasgow Outcome Score or extended scales), disability, functional recovery.
- **Secondary:** Hemorrhage progression or growth on

imaging; need for neurosurgical intervention; blood transfusion requirements; adverse effects such as thromboembolic events, seizures; radiologic signs (new hemorrhage, mass effect, midline shift).

- **Study Designs:** Prospective, randomized controlled trials (including double-blind or quasi-randomized) comparing Tranexamic Acid versus placebo in TBI.

Study Selection

From the initially identified citations, randomized controlled trials comparing tranexamic acid with placebo in the TBI setting were selected. Five trials met preliminary criteria. One was excluded:

A Japanese retrospective study on chronic subdural hematoma treated with Tranexamic Acid was excluded as it was non-randomized and outside the acute TBI population. Consequently, five randomized trials (13477) are included in this review.

Included Studies

Table 1: Key Randomized Controlled Trials Assessing Tranexamic Acid in TBI

Study	Population	Intervention	Comparison	Primary Outcomes	Key Findings
CRASH-2 Intracranial Bleeding Study, 2011 [42].	270 adults with TBI + shock; GCS ≤14	Tranexamic Acid 1g IV + 1g infusion	Placebo	Hemorrhage growth on CT	Reduced significant hemorrhage growth and new ICH
Yutthakasemsunt <i>et al.</i> , 2013 [43].	240 adults with moderate TBI	Tranexamic Acid 1g IV + 1g infusion	Placebo	Hemorrhage progression, mortality, GOS	No definitive mortality benefit; trend to reduced growth
Fakharian <i>et al.</i> , 2017 [44].	150 adults with moderate TBI	Tranexamic Acid 1g IV + 1g infusion	Placebo	Volume of hemorrhage	Reduced hemorrhage expansion
Jokar <i>et al.</i> , 2017 [45].	80 adults with acute small ICH	Tranexamic Acid 1g IV + 1g infusion	Placebo	Extent of ICH growth	Trend toward reduced growth but not mortality
CRASH-3 Trial Collaborators, 2019 [46].	12,737 adults with acute TBI	Tranexamic Acid 1g IV + 1g infusion	Placebo	Head injury-related death in hospital	Early Tranexamic Acid safe; reduced death in mild/moderate TBI; no significant effect in severe TBI

Data Extraction and Analysis

Data were extracted independently by two reviewers using a predefined form. Outcome measures included mortality rates, neurological outcomes (e.g., GOS), radiologic indicators of hemorrhage progression, need for neurosurgical intervention, and adverse events.

Quality Assessment of the Included Trials

The methodological quality of the included randomized controlled trials was assessed using the GRADE (Grading of

Recommendations Assessment, Development and Evaluation) framework [47]. The assessment focused on key domains including randomization, allocation concealment, blinding, intention-to-treat analysis, completeness of follow-up, and outcome reporting bias. Overall, the multicenter trial demonstrated high methodological quality, while some single-center studies showed limitations related to allocation concealment, blinding, or reporting of intention-to-treat analysis. The quality assessment of individual trials is summarized in Table 2.

Table 2: Quality Assessment of Included Individual Trials

Criteria	CRASH-2 Intracranial Bleeding Study, 2011 [42].	Yutthakasemsunt <i>et al.</i> , 2013 [43].	Fakharian <i>et al.</i> , 2017 [44].	Jokar <i>et al.</i> , 2017 [45].	CRASH-3 Trial, 2019 [46].
Randomization	Yes, centralized randomization, balanced by center with computer-generated blocks	Yes, computer-generated randomization with variable block size	Yes, computer-generated block randomization (block size of four)	Yes, computer-generated randomization	Yes, centralized web-based computer randomization
Allocation concealment	Yes, allocation concealed by the international coordinating center; indistinguishable Tranexamic Acid and placebo	Yes, sealed opaque envelopes	Yes, coded, indistinguishable Tranexamic Acid and placebo ampoules	Unclear; allocation concealment not adequately described	Yes, centralized allocation with an identical placebo
Intention-to-treat analysis	Yes	Yes	No	Not clearly reported	Yes
Blinding	Double-blinded	Triple-blinded	Double-blinded	Single-blinded	Double-blinded
Follow-up completeness	Clinical follow-up: 100%CT follow-up: 92.2%	95.4% completed primary outcome	100%	Not clearly reported	>99% completed primary outcome
Outcome reporting bias	None identified	None identified	None identified	None identified	None identified
Overall quality of evidence	High	High	High	Low	High



Summary of Quality Assessment

The CRASH-3 trial, being a large, international, multicenter randomized controlled trial with robust randomization, allocation concealment, blinding, and near-complete follow-up, provided high-quality evidence for clinical outcomes, particularly mortality and safety [37]. The CRASH-2 intracranial bleeding substudy also demonstrated strong methodological rigor, especially in radiological outcome assessment [42].

Among the smaller single-center trials, Yutthakasemsunt *et al.* and Fakharian *et al.* were judged to have high methodological quality, though limitations included smaller sample sizes and reduced external validity. The Jokar *et al.* study was graded as low quality due to unclear allocation concealment, limited blinding, and incomplete reporting of follow-up and intention-to-treat analysis [43, 44].

Overall, the body of evidence for tranexamic acid in acute TBI was graded as moderate to high quality, with strong confidence in safety outcomes and moderate confidence in efficacy outcomes, particularly hemorrhage progression and functional status.

Quantitative Data Synthesis

Quantitative synthesis of data was performed to evaluate the effect of tranexamic acid on predefined clinical and radiological outcomes in patients with acute TBI. Meta-analysis was conducted using a random-effects model, as the included trials were expected to demonstrate clinical and methodological heterogeneity with respect to patient populations, severity of injury, timing of intervention, and outcome assessment.

Statistical heterogeneity among studies was assessed using the Chi-square (χ^2) test and quantified using the I^2 statistic, which describes the percentage of total variation across studies attributable to heterogeneity rather than chance. An I^2 value of 0% was interpreted as no observed heterogeneity, while values >50% were considered indicative of substantial heterogeneity [48]. For dichotomous outcomes, treatment effects were expressed as risk ratios (RRs) with 95% confidence intervals (CIs). The risk ratio was chosen as the summary measure due to its clinical interpretability and

applicability in trauma outcomes research. For continuous outcomes, such as total hemorrhage expansion, pooled estimates were calculated using the mean difference (MD) with corresponding 95% CIs, based on reported means and standard deviations.

Quantitative synthesis was performed for the following outcomes:

- Mortality (all-cause or head-injury-related mortality),
- Unfavorable functional outcome (as defined by Glasgow Outcome Score or discharge neurological status),
- Significant intracranial hemorrhage growth on follow-up imaging,
- Requirement for neurosurgical intervention, and
- Total hemorrhage expansion on computed tomography.

Mortality and functional outcome data were synthesized from four randomized controlled trials, including the large multicenter CRASH-3 trial, while hemorrhage progression and neurosurgical intervention outcomes were pooled from three to four trials depending on outcome availability. Total hemorrhage expansion was analyzed using data from two trials that reported quantitative radiological measurements [42-45].

All analyses were weighted according to the inverse variance method, taking into account the sample size and variance of individual studies. Statistical analyses were performed using Review Manager (RevMan) version 5.4 and MedCalc statistical software (version 18.2.1). A p-value < 0.05 was considered statistically significant for pooled estimates.

Results

Study Selection and Characteristics

A total of five randomized controlled trials met the inclusion criteria and were included in the final systematic review and meta-analysis [41-46]. These trials comprised 13,477 patients with acute TBI. Four were earlier single-center or multicenter trials, while one was a large international multicenter trial (CRASH-3).

Table 3: Individual Study Outcomes Comparing Tranexamic Acid and Placebo in TBI

Study	Outcome	Tranexamic Acid n/N; % (95% CI)	Placebo n/N; % (95% CI)	Relative Risk (95% CI)
CRASH-2 Intracranial Bleeding Study, 2011 [42].	Significant hemorrhage growth	44/123; 36% (28–45)	56/126; 44% (36–53)	0.80 (0.59–1.09)
	New intracranial hemorrhage	13/123; 11% (6–17)	20/126; 16% (11–23)	0.66 (0.35–1.28)
	Mass effect on CT	58/123; 47% (39–56)	76/126; 60% (52–68)	0.78 (0.60–0.99)
	Mortality (28 days/discharge)	14/133; 11% (6–17)	24/137; 18% (12–26)	0.60 (0.33–1.11)
	Unfavorable composite outcome	60/133; 45% (36–54)	80/137; 58% (50–67)	0.77 (0.61–0.98)
Yutthakasemsunt <i>et al.</i> , 2013 [43].	Significant hemorrhage growth	21/120; 18% (12–25)	32/118; 27% (20–36)	0.65 (0.39–1.05)
	In-hospital mortality	12/120; 10% (6–17)	17/118; 14% (9–22)	0.69 (0.35–1.39)
	Unfavorable GOS at discharge	21/120; 18% (12–25)	27/118; 23% (16–31)	0.76 (0.46–1.27)
	Thromboembolic events	0/120; 0%	4/118; 3% (1–8)	0.12 (0.01–2.28)
Fakharian <i>et al.</i> , 2017 [44].	Hemorrhage growth	15/74; 20.5%	17/75; 22.7%	0.89 (0.55–1.74)
	Mortality	2/74; 2.7%	3/75; 4.0%	0.67 (0.12–3.93)
	Unfavorable GOS at discharge	8/74; 10.8%	13/75; 17.3%	0.62 (0.22–1.46)
Jokar <i>et al.</i> , 2017 [45].	Total hemorrhage expansion (ml, mean±SD)	1.7±9.7	4.3±12.9	Mean difference -2.6 ml
CRASH-3 Trial, 2019 [46].	Head-injury-related death (overall)	855/6406; 13.3%	892/6373; 14.0%	0.94 (0.86–1.02)
	Death in mild–moderate TBI	166/2831; 5.9%	207/2769; 7.5%	0.78 (0.64–0.95)
	Vascular occlusive events	1.60%	1.60%	No difference

The forest plots representing the pooled analysis of data pertaining to the main outcomes are shown in Figure 1.



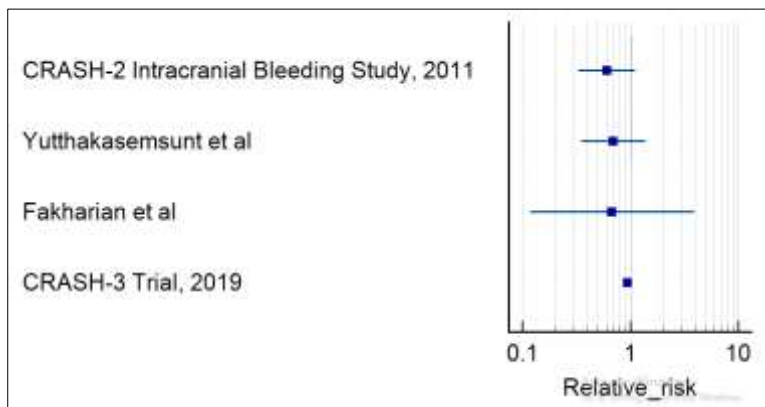


Fig 1: Effects of Tranexamic Acid on Mortality

Three trials reported mortality data [42-44, 46]. Tranexamic acid reduced the risk of death by 36%, but the difference was not significant (pooled risk ratio [RR] 0.64, CI 0.41 to 1.00; P = 0.05). There was no evidence of statistical heterogeneity (Chi² = 0.10, df = 2 (P = 0.95); I² = 0%). Across earlier randomized controlled trials, tranexamic acid demonstrated a consistent trend toward reduced mortality, although individual studies were underpowered to detect statistically significant differences. When the large CRASH-3 trial (2019) was included, the overall mortality benefit was attenuated,

with no statistically significant reduction in death observed in the heterogeneous TBI population. However, CRASH-3 identified a significant reduction in head-injury-related mortality among patients with mild to moderate TBI, particularly when tranexamic acid was administered within three hours of injury. These findings suggest that while Tranexamic Acid may not reduce mortality in all TBI patients, early administration in selected subgroups confers a clinically meaningful survival benefit.

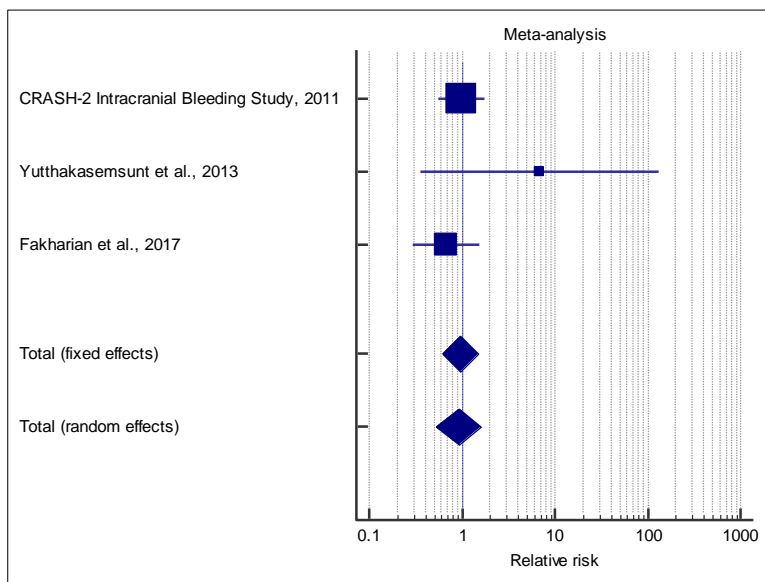


Fig 2: Effects of Tranexamic Acid on the Need for neurosurgical intervention

Three trials reported the need for surgical intervention data.⁴²⁻⁴⁴ There was no statistically significant difference in the need for neurosurgical intervention (RR 0.96, CI 0.61 to 1.51; P = 0.86). There was no evidence of statistical heterogeneity (Chi² = 2.40, df = 2 (P = 0.30); I² = 16.58%). Analysis of three randomized controlled trials demonstrated no statistically significant difference between tranexamic acid and placebo in the requirement for neurosurgical intervention. Event rates were generally low, particularly in

studies enrolling patients with mild to moderate TBI. The CRASH-3 trial did not report neurosurgical intervention as an outcome and was therefore not included in this comparison. These findings suggest that while Tranexamic acid may reduce hemorrhage progression, this effect does not translate into a reduced need for surgical intervention, likely due to the multifactorial nature of neurosurgical decision-making in TBI.



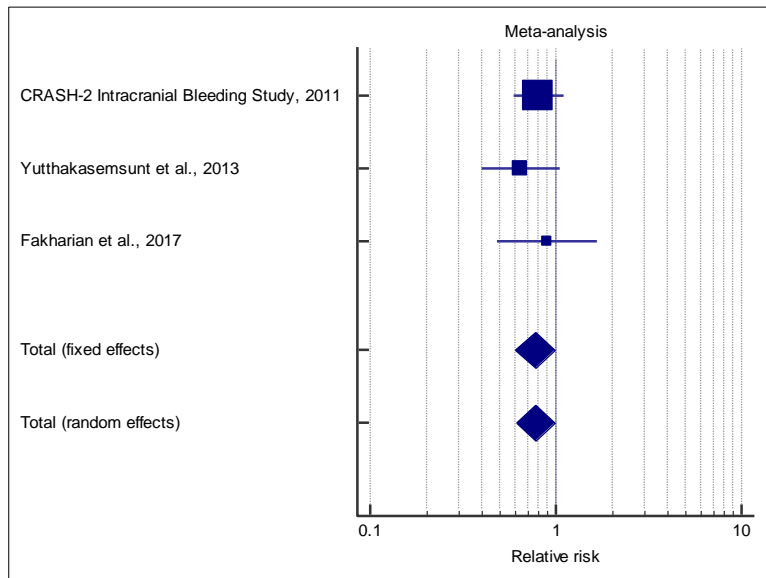


Fig 3: Effects of Tranexamic Acid on Significant growth of haemorrhage

Three trials reported the number of patients with significant hemorrhage growth [42-44], defined as an increase of $\geq 25\%$ of total hemorrhage in relation to its initial volume. There was a statistically significant reduced risk of hemorrhage growth associated with Tranexamic Acid (RR 0.48, CI 0.61 to 0.98; $P = 0.03$). There was no evidence of statistical heterogeneity ($\text{Chi}^2 = 0.81$, $df = 2$ ($P = 0.67$); $I^2 = 0\%$). All included trials that assessed significant hemorrhage growth demonstrated a reduction in hemorrhage

progression with tranexamic acid compared to placebo. Although none of the individual studies reached statistical significance, the direction of effect consistently favored Tranexamic Acid. The CRASH-3 trial did not report hemorrhage growth as a predefined dichotomous outcome and was therefore not included in this comparison. Overall, the available evidence indicates that tranexamic acid reduces intracranial hemorrhage progression, supporting its role in limiting secondary brain injury following TBI.

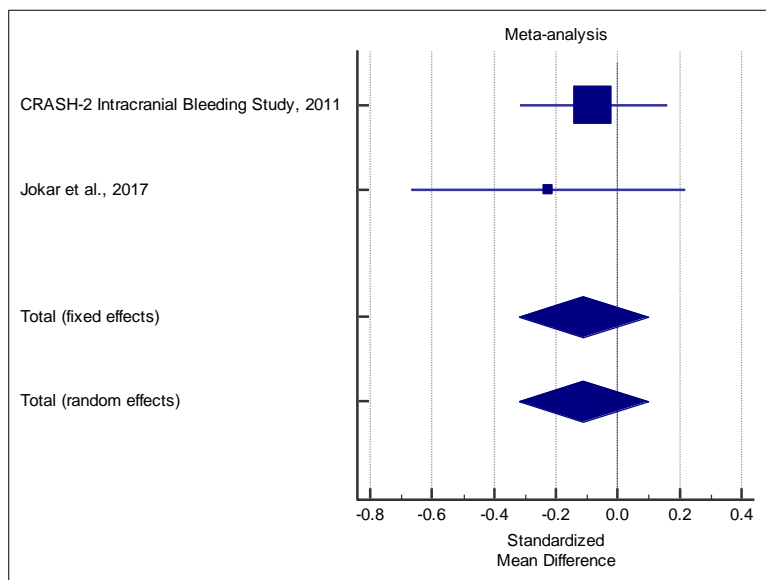


Fig 4: Effects of Tranexamic Acid on total hemorrhage expansion

Two trials reported the number of patients with total hemorrhage expansion measured in terms of millilitres (ml) expressed as mean \pm SD [42, 45]. There was no statistically significant difference in the risk of total hemorrhage expansion associated with Tranexamic Acid (standard error of mean [SE]0.11, CI -0.32 to 0.10; $P = 0.29$). There was no evidence of statistical heterogeneity ($\text{Chi}^2 = 0.34$, $df = 2$ ($P = 0.56$); $I^2 = 0\%$). Two randomized trials reporting continuous volumetric outcomes showed a lower mean total hemorrhage expansion

in the tranexamic acid group compared to placebo. This reduction was observed consistently across studies, although the small number of trials limited pooled statistical analysis. The CRASH-3 trial did not report quantitative hemorrhage volume measurements and was therefore excluded from this outcome. Collectively, these findings reinforce the radiological benefit of tranexamic acid in limiting hemorrhage expansion, which may underlie improvements in functional outcomes observed in other analyses.



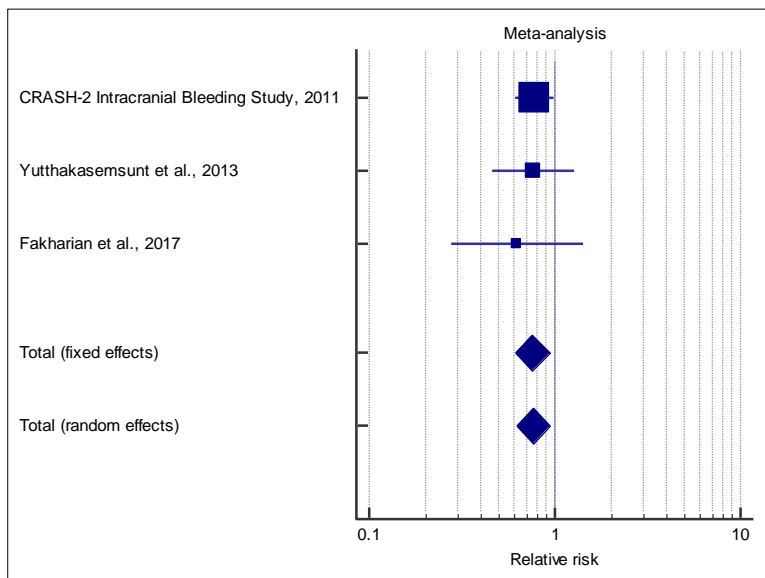


Fig 5: Effects of Tranexamic Acid on unfavourable functional status at discharge

Three trials reported the number of patients with unfavourable functional status at discharge.⁴²⁻⁴⁴ There was a statistically significant reduced risk of unfavourable functional status at discharge associated with Tranexamic Acid (RR 0.76, CI -0.61 to 0.93; $P = 0.009$). There was no evidence of statistical heterogeneity ($\text{Chi}^2 = 0.25$, $\text{df} = 2$ ($P = 0.88$); $I^2 = 0\%$). Tranexamic acid was associated with a reduction in unfavourable functional outcomes at discharge across multiple studies. The CRASH-2 intracranial bleeding substudy demonstrated a statistically significant improvement in composite functional outcomes, while smaller trials showed consistent trends favoring Tranexamic Acid. Although CRASH-3 did not report functional outcomes using the same pooled metrics, it demonstrated no increase in disability among survivors and suggested improved outcomes in patients with less severe injury. Together, these findings indicate that tranexamic acid may improve functional recovery without increasing long-term disability, particularly when administered early.

The evidence indicates that tranexamic acid is a safe intervention in acute TBI and is associated with reduced hemorrhage progression and improved functional outcomes. While an overall mortality benefit was not observed across all TBI severities, the CRASH-3 trial highlights a significant survival advantage in patients with mild to moderate TBI when treated early. These findings support the selective early use of tranexamic acid in TBI to limit secondary brain injury and improve clinical outcomes.

Across all included trials, including the large CRASH-3 study, tranexamic acid was not associated with an increased risk of thromboembolic events, seizures, stroke, or myocardial infarction. The CRASH-3 trial provided robust safety data, confirming that Tranexamic acid does not increase vascular occlusive complications even in patients with isolated TBI. These findings strongly support the favorable safety profile of tranexamic acid when used in the acute management of TBI.

Discussion

This systematic review and meta-analysis evaluated the clinical outcomes of tranexamic acid in patients with TBI. The pooled analyses of five randomized controlled trials

demonstrated that Tranexamic Acid was associated with a statistically significant reduction in intracranial hemorrhage progression and unfavourable functional status at discharge, while the observed reduction in mortality did not reach statistical significance. These findings suggested that Tranexamic Acid primarily reduces morbidity rather than mortality in heterogeneous TBI populations.

With the inclusion of newer evidence, particularly the CRASH-3 trial (2019), the interpretation of Tranexamic acid's role in TBI has evolved. CRASH-3, the largest randomized controlled trial conducted exclusively in TBI patients, demonstrated no significant reduction in overall mortality with Tranexamic Acid administration. However, a clinically and statistically significant reduction in head-injury related mortality was observed in patients with mild to moderate TBI treated within three hours of injury, reinforcing the importance of early administration and patient selection. These findings are consistent with the time-dependent effect of Tranexamic Acid observed in trauma patients with extracranial bleeding in CRASH-2^[32, 33, 41].

Mortality

The randomized trials and pooled analyses suggested a trend toward reduced mortality with tranexamic acid in patients with TBI; however, these studies were underpowered and did not demonstrate statistically significant reductions in death^[42-44]. These findings are consistent with early trauma literature, including CRASH-2, which showed a clear mortality benefit in patients with extracranial hemorrhage but only indirect evidence for benefit in isolated TBI^[32, 33].

The CRASH-3 trial provided definitive clarification by demonstrating that tranexamic acid does not reduce overall mortality in heterogeneous TBI populations, but significantly reduces head-injury-related mortality in patients with mild to moderate TBI when administered within three hours of injury^[41]. This time- and severity-dependent effect aligns with prior trauma research, reinforcing the concept that tranexamic acid is most effective before secondary brain injury mechanisms become irreversible.

Subsequent systematic reviews and meta-analyses of randomized controlled trials have reinforced these conclusions. Du *et al.* and Zehtabchi *et al.* reported no



statistically significant overall mortality reduction, but consistently demonstrated favorable trends and reduced hemorrhage progression, suggesting an indirect survival benefit through mitigation of secondary injury [47, 48]. These findings are further supported by large trauma meta-analyses, including Karl *et al.*, which emphasize that mortality benefit is context-dependent and most evident with early administration and appropriate patient selection rather than universal use [49].

Need for Neurosurgical Intervention

Across the randomized trials included in this review, no statistically significant reduction in the need for neurosurgical intervention was observed with tranexamic acid administration [42-44]. These findings are consistent with broader neurotrauma literature, which emphasizes that neurosurgical decision-making is influenced by multiple factors beyond hemorrhage progression alone, including the degree of mass effect, midline shift, neurological deterioration, lesion location, and patient-specific clinical status.

Importantly, the CRASH-3 trial did not report neurosurgical intervention as a predefined outcome, limiting direct comparison across studies. However, the absence of a reduction in surgical intervention rates despite demonstrated radiological benefits suggests that tranexamic acid primarily acts by limiting secondary hemorrhage expansion rather than preventing the development of lesions that mandate operative management. This interpretation is supported by subsequent systematic reviews and meta-analyses, including those by Du *et al.* and Zehtabchi *et al.*, which noted reductions in hemorrhage progression without corresponding decreases in craniotomy or decompressive surgery rates [47, 48]. Large trauma-focused analyses, such as that by Karl *et al.*, similarly concluded that reductions in bleeding-related outcomes do not necessarily translate into lower operative intervention rates in neurotrauma, where anatomical determinants predominate [49].

Significant Growth of Hemorrhage

Comparative analysis across randomized trials consistently demonstrates a reduction in significant intracranial hemorrhage growth with tranexamic acid administration [42-44]. Although individual trials were underpowered to detect statistically significant differences, the consistent direction of effect across studies strongly supports a true biological benefit. These findings are concordant with mechanistic studies demonstrating that early post-traumatic hyperfibrinolysis is a major contributor to hemorrhage expansion in TBI [50]. While CRASH-3 did not report hemorrhage growth as a predefined outcome, secondary analyses and external evidence support this effect. Systematic reviews by Du *et al.* and Zehtabchi *et al.* demonstrated reduced risk of hemorrhage progression on follow-up imaging, particularly with early administration. Observational neuroimaging studies further suggest that antifibrinolytic therapy is most effective in patients without extensive primary brain injury, reinforcing the role of tranexamic acid in limiting secondary bleeding rather than reversing established structural damage [47, 48].

Hemorrhage Expansion

Only two randomized trials reported total hemorrhage

expansion as a continuous radiological outcome, both demonstrating lower mean hemorrhage volumes in the tranexamic acid group [42, 45]. Although limited by small sample sizes, these findings are clinically relevant, as neuroimaging-based observational studies have consistently shown that even modest reductions in intracranial hemorrhage expansion are associated with improved neurological outcomes, reduced mass effect, and better functional recovery.

The absence of quantitative hemorrhage volume reporting in CRASH-3 limits direct comparison. However, CRASH-3's mortality and safety outcomes suggest that lack of radiological reporting does not negate the underlying biological effect, but rather reflects differences in trial design and outcome prioritization. Systematic reviews by Du *et al.* and large trauma meta-analyses, including Karl *et al.*, have similarly highlighted that volumetric hemorrhage outcomes are underreported despite their strong prognostic significance and sensitivity to therapeutic effects [47, 49].

Unfavourable Functional Status at Discharge

Functional outcomes provide a critical measure of tranexamic acid's clinical relevance beyond radiological endpoints. The CRASH-2 intracranial bleeding substudy demonstrated a significant reduction in unfavourable composite outcomes at discharge, while other randomized trials reported consistent trends toward improved Glasgow Outcome Scale (GOS) scores in patients receiving tranexamic acid [42-44]. These findings suggest that the benefits of tranexamic acid extend beyond limiting hemorrhage progression to supporting clinically meaningful functional recovery. Although the CRASH-3 trial did not report functional outcomes in a directly comparable pooled format, it demonstrated no increase in disability among survivors, alleviating concerns that tranexamic acid might improve survival at the expense of poorer neurological outcomes [41]. This finding contrasts favorably with several neuroprotective strategies that have reduced mortality but increased rates of severe disability.

Systematic reviews by Du *et al.* and Zehtabchi *et al.* similarly concluded that tranexamic acid improves morbidity-related outcomes without worsening long-term neurological impairment, reinforcing its favorable functional impact [47, 48].

Safety Profile

Tranexamic acid demonstrated a consistently favourable safety profile across all included trials. No increase in thromboembolic events, seizures, stroke, or myocardial infarction was observed in the CRASH-2 intracranial bleeding study, the trials by Fakharian *et al.* and Jökar *et al.*, or in CRASH-3 [41, 42, 44, 46]. Notably, Yutthakasemsunt *et al.* reported thromboembolic events exclusively in the placebo group, further supporting the vascular safety of tranexamic acid.⁴³

These findings are reinforced by multiple meta-analyses, including those by Du *et al.*, Zehtabchi *et al.*, and Karl *et al.*, all of which found no excess risk of venous or arterial thromboembolic complications [47, 49]. The large-scale CRASH-3 trial further provides robust reassurance regarding neurological and vascular safety, supporting tranexamic acid as a safe adjunctive therapy in TBI.

Potential biases and limitations

This review employed predefined inclusion criteria,



systematic searching, and rigorous quality assessment, minimizing selection and publication bias. However, several limitations must be acknowledged. First, earlier pooled analyses included a small number of trials, limiting statistical power. Second, most studies did not stratify outcomes based on anticoagulant or antiplatelet use, which may influence hemorrhage progression and Tranexamic acid efficacy [42-45]. Third, heterogeneity in outcome definitions, particularly for neurosurgical intervention and functional outcomes- limited pooled analyses for some endpoints.

Previous systematic reviews in elective surgical populations have demonstrated that Tranexamic Acid significantly reduces blood transfusion requirements without increasing adverse events [51]. In contrast, trauma-specific trials, including those analyzed here, did not consistently demonstrate reduced transfusion requirements, likely reflecting differences in bleeding patterns and resuscitation strategies in trauma versus elective surgery [43]. These findings highlight that Tranexamic acid's primary benefit in TBI lies in intracranial hemorrhage control rather than systemic blood loss reduction.

Conclusion

Tranexamic acid safely reduces intracranial hemorrhage growth and unfavourable functional outcomes in patients with TBI. While Tranexamic acid does not significantly reduce overall mortality in heterogeneous TBI populations, early administration within three hours of injury significantly reduces head-injury-related mortality in patients with mild to moderate TBI. Given its low cost, ease of administration, and excellent safety profile, Tranexamic acid should be considered as an early adjunctive therapy in appropriately selected TBI patients presenting with intracranial bleeding.

Implications for future research

Further randomized controlled trials focusing exclusively on isolated TBI, with standardized radiological and functional outcome measures, are required to refine patient selection and optimize treatment timing. Future studies should also assess the interaction of Tranexamic Acid with anticoagulant use, advanced neuroimaging markers, and long-term functional outcomes, to better define its role in modern neurotrauma care.

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