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The Impact of Pre-hospital use of Tranexamic Acid (TXA) in patients with acute Traumatic Brain Injury (TBI)

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- **Abstract**

Background: Traumatic brain injury (TBI) is a critical medical condition that has a substantial influence on healthcare systems worldwide. Effective management in pre-hospital settings is essential for enhancing patients outcomes. The efficacy of Tranexamic acid (TXA) in reducing mortality and transfusions in hemorrhagic conditions has been proven. The aim of this systematic review is to assess the effectiveness and safety of TXA administration in the pre-hospital phase of TBI management. The review will specifically examine mortality rates, functional outcomes, and adverse events associated with the use of TXA in TBI patients.
Methods: A search was conducted through five electronic databases until May 30, 2023. The study used a search protocol that utilized relevant keywords related to the research question to identify randomized controlled trials, case-control studies, and observational studies published in English since 2018. The studies were focused on assessing the effects of TXA administration in pre-hospital settings for patients with traumatic brain injury. The analysis takes into account specific patient outcomes such as mortality rate, neurological function, and complication risk.
Results: Five studies out of 304 were included, involving 7503 participants. One of them was high-quality RCT, and four were retrospective observational studies, three of which were of high quality and one with a high risk of bias. All the included studies reported the primary outcome and showed no mortality benefits, except in one study, which showed an increase in mortality in isolated TBI patients. Secondary outcomes demonstrated no differences in functional outcomes and no further complication risks in TBI patients who received TXA in pre-hospital settings.
Conclusion: Most studies reported no difference in the results of the administration of TXA in TBI patients; however, there was a significant difference in mortality with isolated TBI. Further studies need to be done on patients with isolated TBI and different TXA doses. As it is an area where the practice may change.

1. Introduction

As part of the Master's program in critical care, this dissertation is a systematic review that will discuss the impact of pre-hospital administration of tranexamic acid (TXA) in patients with acute traumatic brain injury (TBI) on the mortality rate. The introduction, methodology, results, discussion, conclusion, and references are the main sections of this dissertation. I will begin with the introduction, which provides an outline of the study issue, expresses the research question, states the aim and objectives, and explains the rationale behind conducting this review. In the method section, information was reported about the search protocol, study selection criteria, data extraction processes, and quality assessment tools. Next, in the results, a summary of the features of the included studies will be written, and the findings of the included studies will be presented in tables. Additionally, the discussion section interrupts the findings, evaluates their strengths and limitations, compares them to previous relevant studies, and highlights research gaps to draw possible recommendations. A succinct overview will be provided in the conclusion, with an emphasis on the significance of the research in clinical practice. Finally, all sources used in the dissertation are listed in the references section using the same citation format.

➢ 1.1 Description of the condition

○ *Head injury*

Head injury is a worldwide public health issue that affects an estimated 69 million people globally each year, based on World Health Organization (WHO) records. The prevalence of head injury varies among populations as it depends on several factors, including age, gender, occupation, alcohol and substance misuse, and engagement in extreme sports or hazardous activities, all of which are considered potential contributors to an increased risk of head injury (1). A

head injury is defined as damage that affects the head, including the scalp, face, skull, and underlying structures. induced by external physical force or trauma applied to the head. Falls, road traffic accidents (RTAs), assaults, sports-related injuries, and other types of physical violations are examples of many potential causes of head injuries. The consequences of a head injury vary based on different factors, including the location, type, and severity of the injury. There are serious consequences that can result from head injuries, including traumatic brain injury and associated hemorrhage, intracranially or extracranially (2).

- ***Traumatic brain injury***

The term "traumatic brain injury" (TBI) refers to brain damage resulting from external force. TBI is divided into two types: primary and secondary injuries, which refer to different mechanisms and processes that lead to brain damage and its consequences. Primary injury is the immediate physical damage to the brain as an impact of external force, which interrupts normal brain function and leads to acute neurological symptoms. Primary TBI can include lacerations, conctusions, and diffuse axonal injury (3). Secondary injury is the serious physiological and biochemical consequences that arise following the primary insult in hours, weeks, and days. Moreover, it can aggregate the damage from the primary injury and greatly affect the long-term TBI prognosis. The damage caused by secondary injury is obtained through several possible mechanisms, including excitotoxicity, brain swelling, decreased blood flow, oxidative stress, and cell death. Additionally, intracranial pressure (ICP) increases and causes compression of the brain structure as a result of the injury, which causes further cell damage, neurological impairment, and long-lasting complications (Figure1)(4).

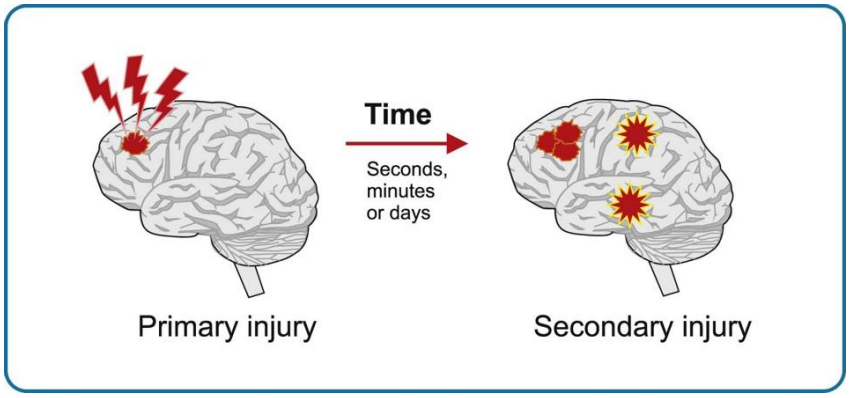


Figure 1: A brief description of the progression of TBI

- ***Intracranial hemorrhage (ICH)***

As a result of primary or secondary TBI, various types of intracranial bleeding can occur. Intracranial bleeding is the term for bleeding within the cranial cavity inside the skull, which is caused by bleeding within or around the brain tissue. For instance, head injuries can result in one or more types of intracranial bleeding, such as epidural hematoma, subdural hematoma, subarachnoid hemorrhage, intracerebral hemorrhage, contusion, and diffuse axonal injury. However, intracranial bleeding is not considered a secondary brain injury, but it can contribute to the secondary TBI process (Figure 2)(5).

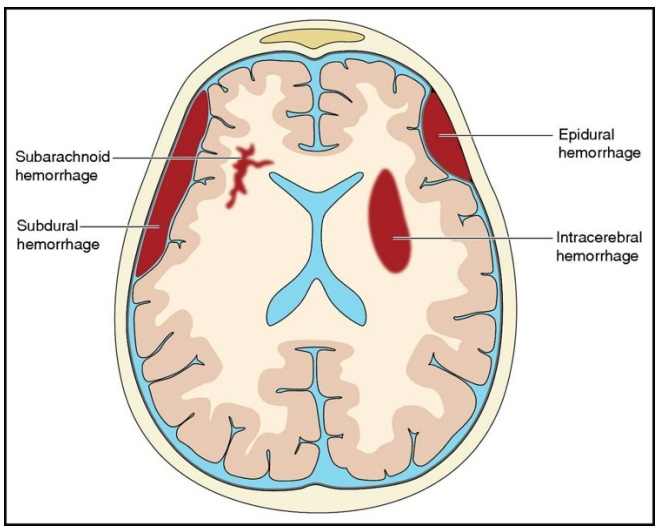


Figure 2: A demonstration of the various types of intracranial hemorrhage

- ***Extracranial hemorrhage (ECH)***

Extracranial bleeding results from a head injury. It refers to the bleeding that occurs outside the skull, which involves bleeding from the blood vessels, tissues, or organs surrounding the skull rather than within the brain. In extracranial hemorrhage, highly vascular tissues are more prone to bleeding due to the plentiful blood supply they have. Moreover, vascularity levels vary among people as they may be affected by several factors, such as age, overall health, and underlying medical disorders. The scalp, face, nasal cavity, and oral cavity are all examples of highly vascular tissues in the head. Scalp lacerations can lead to excessive bleeding due to the abundance of blood vessels supplying the scalp. Additionally, damage or rupture in the nasal or oral cavity vessels is dangerous not just regarding blood volume loss but also to the airway, which in excessive cases can cause aspiration (6).

- ***TBI Severity classifications***

Depending on the amount of damage and the patient's clinical presentation, head injuries are often categorized into three different levels, which range from mild to severe. The Glasgow Coma Scale (GCS) is a standard tool for determining the severity of brain injury by evaluating the level of consciousness by measuring three types of responses: eye-opening response, verbal response, and motor response. Each area is given a score, which is then added together to get an overall GCS score from 3 to 15, as the minimum score in each domain is 1 (7).

The following criteria are used to differentiate between different levels of TBI severity:

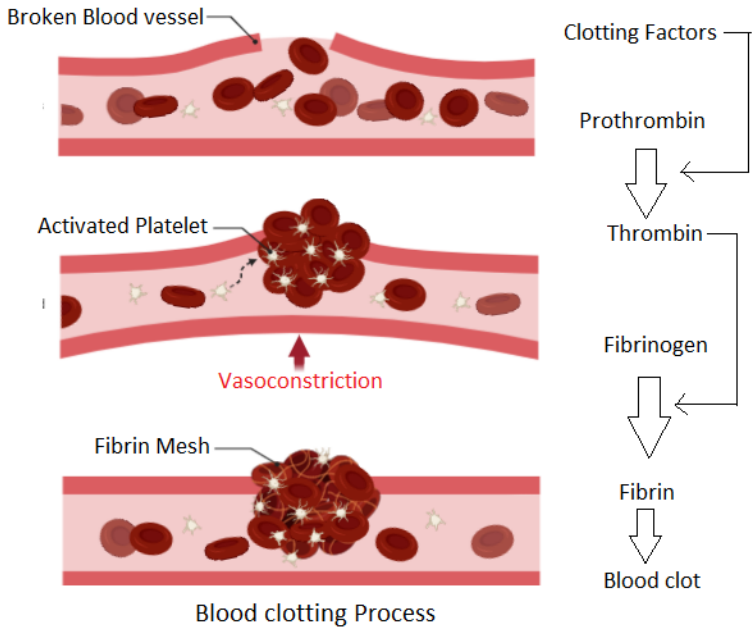
- ***Mild TBI*** refers to patients with a GCS of 13 to 15 who have a history of a brief loss of consciousness, disorientation, dizziness, nausea, or post-traumatic amnesia (8).
- ***Moderate TBI*** is defined by a GCS score of 9 to 12 and physical signs such as abnormal motor responses, localized neurological impairments,

and skull fractures. They frequently demonstrate more significant changes in consciousness, such as a prolonged duration of confusion or losing consciousness for up to several minutes.

- ***Severe TBI*** is characterized by a GCS score of 8 or below. Patients in this category often lose consciousness for more than six hours at a time and have other serious symptoms, such as cognitive impairment or coma. Moreover, substantial neurological abnormalities, irregular respiratory patterns, and abnormal posturing are all considered signs of severe brain injury (9).

- **Trauma-induced coagulopathy**

Trauma-induced coagulopathy is an extensive condition that arises due to excessive bleeding in response to a traumatic event. When trauma occurs, the body immediately activates physiological responses to manage the bleeding, these responses include vasoconstriction, platelet aggregation, clot formation, and the release of inflammatory mediators (Figure 3)(10).



Blood clotting Process

Figure 3: An illustration of Hemostasis, which refers to the physiological response of the body to an injury that results in bleeding. This physiological response stops hemorrhage and initiates the process of wound healing within the body.

However, trauma-induced bleeding can disrupt the normal coagulation cascade, which results in coagulopathy. Trauma-induced coagulopathy is a condition when the normal coagulation cascade is interrupted by different mechanisms, including the consumption and dilution of platelets and clotting factors, tissue damage caused by hypoperfusion, and the release of fibrinolytic enzymes. The disturbance in the coagulation system can lead to inadequate clot formation, which leads to further bleeding. Understanding the pathophysiological mechanisms underlying trauma-induced coagulopathy is of the utmost significance in the effective management of traumatic injuries (11, 12). This is because Coagulopathy is directly linked to the trauma triad of death, which consists of coagulopathy, acidosis, and hypothermia. These interrelated conditions exacerbate each other in individuals with severe trauma, resulting in further complications and worse outcomes (Figure 4). Therefore, the implementation of focused interventions, such as the utilization of tranexamic acid (TXA), activities to reestablish balance between coagulation and fibrinolysis, thereby diminishing hemorrhaging as well as improving results (13).

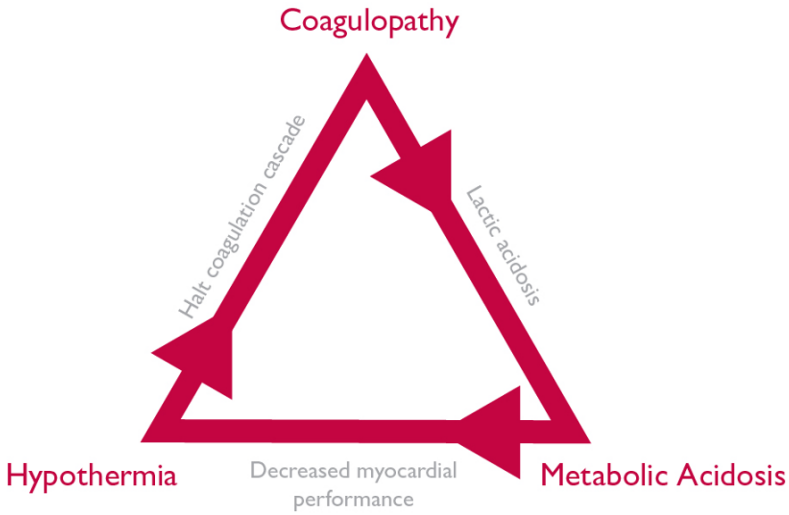


Figure 4: The components of the triad of death

- **Functional status assessment**

Functional assessment scores are frequently utilized for traumatic brain injuries to evaluate various aspects of functional outcomes after the injury, such as GOS and DRS. The choice of an appropriate scale is dependent on the purpose and context of the evaluation.

- ***Glasgow Outcome Scale (GOS)***

The GOS score is a commonly employed assessment tool for assessing functional outcomes among individuals who have sustained TBIs. The patients are classified into five distinct groups based on their degree of dependence and disability, which span from death to complete recovery. The GOS offers a uniform method of evaluating the overall outcome of TBI patients, enabling healthcare providers to classify patients based on their functional status and their level of independence in routine activities (14).

- ***Disability rating score (DRS)***

The DRS is utilized to evaluate the level of functional disability among patients who have sustained TBIs, assess the impact of the injury, and guide optimum treatment. The assessment measures an individual's cognitive, communication, motor, and daily routine activity skills. Each item is assigned a score, with higher scores indicating a greater degree of disability. The DRS generally falls within the range of 0 (without disability) to 30 (death), as higher scores are indicative of more significant impairment (15).

1.2 Description of the Intervention

- **Tranexamic acid**
- ***Mechanism of action***

Tranexamic acid, also known as TXA, is a lysine-derived synthetic compound that works as an antifibrinolytic agent and is classified as a lysine analogue. It binds to the lysine receptor to inhibit the binding of plasmin to the same receptor, as plasmin binding is responsible for fibrinolysis. Therefore, TXA binding plays an important role in preventing the breakdown of blood clots and maintaining the strength of clots by stabilizing the fibrin matrix without promoting the formation of new blood clots. TXA is mainly used to prevent excessive bleeding and stabilize clotting formation in the early phases of trauma-induced bleeding. It works best if given as soon as possible after the trauma has occurred (Figure 5)(16).

- ***Indications***

TXA is used to treat bleeding and minimize blood loss in a variety of medical situations, such as trauma-related bleeding, surgical operations, menstrual bleeding disorders, dental treatment, and hemorrhagic disorders.

In pre-hospital settings, TXA is used for specific conditions that will benefit from early administration, including trauma patients who have serious injuries or patients with suspected internal bleeding.

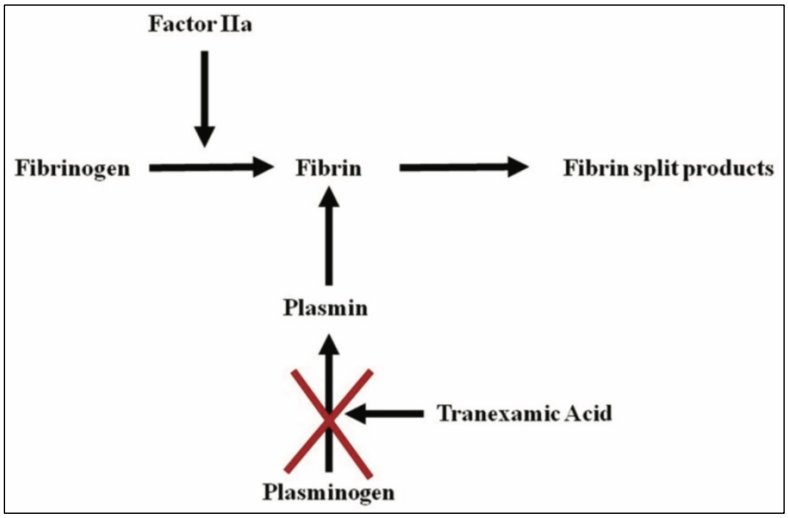


Figure 5: The mechanism of action of tranexamic acid within the coagulation cascade

- ***Dosage and administration***

The recommended pre-hospital dosage for adult patients of TXA is 1 g as a loading dose intravenously (IV) over 10 minutes in trauma-induced bleeding. A second dose of TXA can be given IV over the next 8 hours (17).

- **Monitoring and follow-up**

Following the administration of TXA, it is crucial to monitor the patient's hemodynamic status for any potential side effects or adverse reactions, including thromboembolic events and allergic reactions. Some side effects of using TXA include diarrhea, seizures, headaches, abdominal pain, nausea, vomiting, and visual disturbances.

It is important to note that TXA has a half-life of 2 to 11 hours and an onset of action of 3 hours.

- **Contraindications**

Prior to the administration of TXA, it is important to take into account its contraindications. It is contraindicated in patients who exhibit hypersensitivity or allergic reactions to TXA, patients who have active thromboembolic events, such as deep vein thrombosis (DVT) or pulmonary embolism (PE), patients with color vision disturbances, and patients with subarachnoid hemorrhage. Furthermore, administration of TXA beyond a 3-hour window from the time of TBI is contraindicated. Extreme caution should be exercised while treating patients with TXA who have previous allergic conditions, and alternative treatment options may need to be considered (18).

➢ 1.3 How the intervention might work

A potentially fatal complication of traumatic brain injury is intracranial hemorrhage, particularly if it develops during the first 24 hours after the

traumatic insult, which occurs more likely in people with severe TBI with a rate of 25% to 45%, while the incidence rates for moderate TBI are 3% to 12% and for mild TBI are 0.2% (19). Furthermore, there is a strong correlation between ICH and coagulopathy, which in turn increases the likelihood of the progression of the bleeding and increases mortality risk (20). There was evidence that this bleeding can develop or persist after a patient is admitted to the hospital, known as delayed enlargement of ICH, which is the most frequent cause of clinical deterioration and a poorer prognosis, especially in patients who experienced a lucid interval after TBI (21). Paramedics in the prehospital setting possess a distinct opportunity to administer treatment to patients during the critical "golden hour" of trauma care. It is widely agreed that prompt and effective intervention during this period can significantly enhance patient outcomes. Hence, early administration of an antifibrinolytic agent in a pre-hospital environment may potentially decrease the risk of complications in patients with traumatic brain injury. Recent studies have demonstrated the efficacy of tranexamic acid as an antifibrinolytic drug in the treatment of excessive bleeding caused by trauma (22).

- **The use of TXA in trauma patients with excessive bleeding**

A well-known randomized controlled trial (CRASH-2) was published in 2010 that included over 20,000 participants from 40 different countries who were trauma victims at high risk of significant bleeding. In CRASH-2, patients were randomly allocated and given TXA or a placebo within a time frame of 8 hours from the initial insult. The main endpoint used to evaluate the trial's results was the incidence of mortality due to any cause within a period of 28 days. According to the results of CRASH-2, TXA considerably decreased the risk of death from bleeding. It was proven that the TXA group had a 14.5% mortality rate, while the placebo group had a 16.0% mortality rate. The trial concluded that when TXA was given within 3 hours of the injury, the mortality rate

dropped significantly (Table 1). However, the trial covered a diverse population of trauma patients, thereby posing a challenge in identifying the particular subcategories that may derive the greatest benefit from the TXA administration. Furthermore, the trial mainly emphasized mortality outcomes without evaluating other clinical outcomes, such as possible complications and long-term functional outcomes (23).

It is a fact that CRASH-2 received significant media attention due to its implications for trauma management and the use of TXA in reducing bleeding-related mortality.

- **The use of TXA in TBI - in hospital settings**

Recently, another large international randomized controlled trial known as the CRASH-3 trial was published in 2019, which enrolled over 12,000 adult patients with TBI from 29 countries and investigated the use of TXA in this population. This trial used observations and suggestions from CRASH-2 to guide the process of CRASH-3 to improve and target focused outcomes. In CRASH-3, only patients with acute TBI were included for early administration of the TXA within 3 hours from the time of injury in the emergency department (ER). Furthermore, the CRASH-3 evaluated head injury-related mortality in TBI patients as well as functional outcomes using the Glasgow Outcome Scale (GOS) at six months post-injury. The results of the CRASH-3 trial indicate that the administration of TXA did not result in a significant reduction in mortality due to head injury in severe TBI patients or a significant difference in functional outcomes as a whole, except in mild to moderate TBI, where there was a significant reduction in the death rate. The findings suggest that the administration of TXA did not yield a definitive improvement or deterioration of functional outcomes among patients with TBI. However, subgroup analysis

suggests that patients with mild to moderate TBI could get benefits from TXA administration (Table 1) (24).

Trial's Name	Population	Intervention	Setting	Outcome: Mortality
CRASH-2 (2010)	Trauma patients with significant hemorrhage	TXA within 8 hours	In hospital	Mortality reduction
CRASH-3 (2019)	TBI patients	TXA within 3 hours	In hospital	There is no difference in mortality for severe TBI. However, there is a decrease in mortality in mild to moderate TBI.

Table 1: A brief comparison of the two trials and their key findings

- **The use of TXA in TBI in pre-hospital settings**

Both previous trials (CRASH-2 and CRASH-3) investigated the effects of TXA administration in hospital settings. A recent multi-center randomized clinical trial by Rowell SE et al. published in 2020 evaluated the impact of the administration of TXA by comparing different dosages (1 g, 2 g, and placebo) within 2 hours in pre-hospital settings in adults with moderate to severe TBI. Favorable neurological function at six months was the primary outcome of the trial. This trial includes five secondary outcomes, which are mortality at 28 days, DSR at 6 months, development of ICH, and any incidence of seizure or thromboembolic event. Regarding the trial's results, 1280 participants were enrolled, but only 966 were included in the analysis. The study showed that there was no statistically significant difference between the two groups in terms of favorable neurological outcomes at 6 months. Furthermore, similar to the CRASH-3 trial, this trial also showed no difference in mortality at 28 days due to any cause (25).

1.4 Why is it important to do this review

The positive results of the CRASH-2 trial, which demonstrated the benefits of TXA in reducing bleeding-related mortality, have sparked additional trials and studies that focus on TXA. The researchers intend to conduct further investigations into the effectiveness, appropriate dosage, and potential benefits of TXA in particular patient groups and clinical settings. Considering the huge number of trials and studies in this area, it is essential to conduct a comprehensive evaluation through a systematic review to provide a clear view.

The first systematic review and meta-analysis were done by Yokobori.S. et al. in 2020, exploring the effects of TXA administration on mortality in patients with TBI. The study includes all published randomized controlled trials about the effects of TXA administration within the first 24 hours of the injury without limited dosage or administration method up to the end of October 2019. The primary outcome of this study is the mortality rate, and the secondary outcomes include neurological outcomes and hemorrhagic or ischemic complications. 7 RCTs were included in this study, including CRASH-3, which had the largest number of participants, and the initial dose of TXA in all RCTs was 1 g. According to the meta-analysis results, the administration of TXA demonstrated a tendency to decrease mortality due to head injuries. However, the outcomes did not reach statistical significance. Furthermore, there was no statistical significance in the incidence of poor neurological function between TXA groups and placebo groups. Finally, it is important to note that this study did not specifically target patients with traumatic brain injury in the pre-hospital environment (26).

- **Rationale**

There is currently a lack of detailed analysis about the most recent outcomes that have been gained from these studies and huge randomized controlled trials that have been published addressing the effects of the administration of tranexamic acid (TXA) in pre-hospital settings for traumatic brain injury (TBI) on mortality, functional outcomes, and potential complications. As most of these studies and trials have been conducted in recent years, a summary that is both systematic and comprehensive is required in order to evaluate the quality and reliability of the evidence that already exists and to fill the knowledge gap in the pre-hospital field (27).

- **Aim**

The aim of this systematic review is to assess the effectiveness of tranexamic acid (TXA) in the treatment of severe traumatic brain injury (TBI) in the pre-hospital setting on patient outcomes.

- **Objectives**:

- ***Primary***:

  - to evaluate and compare studies reporting patient mortality in patients with mild to severe traumatic brain injuries who received TXA in pre-hospital settings.
  - to investigate the contribution of the use of TXA in pre-hospital settings to patient outcomes.

- ***Secondary***:

  - to analyze studies reporting neurological function in patients with a mild to severe traumatic brain injury who received TXA in pre-hospital settings.
  - to determine the complications after using TXA in pre-hospital settings in patients with mild to severe traumatic brain injuries.

2. Methods

This is a systematic review that is intended to give a comprehensive summary of the current evidence related to the research question (28).

- **2.1 Criteria for considering studies for this review**

- ***Eligibility criteria***

As indicated in the Cochrane Handbook, the PICOS model was utilized to formulate the research question for the review and initiate the literature research as follows (29):

- ***Population:*** the participants included in this review are adult patients with a severe traumatic brain injury (TBI) who received tranexamic acid (TXA) in the pre-hospital setting regardless of gender, race, phenotype, origin, and ethnicity.
- ***Intervention:*** all types of administration of TXA, either infusion or injection.
- ***Comparison:*** standard care without the use of TXA
- ***Outcome:*** patient and health outcomes up to 1 month and over 6 months

➢ ***The primary outcome*** is to measure the mortality rate within the follow-up period from all causes.

➢ ***Secondary outcomes*** are to assess neurological function at discharge and over six months, specifically poor neurological outcomes such as persistent vegetative state and severe disability, and to outline possible complications of the use of TXA in pre-hospital settings with traumatic brain injury patients (30).

- ***Studies:*** the included studies are clinical trials and observational studies (only cohort studies and case-control studies are considered). Observational studies were considered because clinical trials in pre-hospital environments pose significant challenges due to the urgent and dynamic nature of emergency care, ethical considerations surrounding informed consent, limited infrastructure and resources, and logistical complexities. Consequently, there is a lack of pre-hospital randomized controlled trials in databases (31).

I searched for English-language studies published in the last 5 years, from January 2019 to May 2023.

2.2 Search methods for the identification of studies

The electronic search was first carried out in March 2023. Different databases and search engines were used, including the Cochrane Library, PubMed, MEDLINE, Embase, and Ovid, to search for included papers. Several keywords combined, including medical subject heading terms (MeSH) related to the topic, such as paramedic intervention, pre-hospital settings, ambulance response, traumatic brain injury (TBI), epidural hematoma, subdural hematoma, intracerebral hematoma, traumatic subarachnoid hemorrhage, brain bleeding, and mild to severe head injury, were used in conjunction with Boolean operators to search for published articles that fit the criteria for inclusion in the review. Additionally, reference lists of the retrieved articles were also examined for details about relevant published articles that could be included (32).

- ***Studies selection***

The search covered articles published up to May 2023. The author determined the eligibility of the articles for inclusion by screening the titles and abstracts of all identified studies during the search process. The papers that clearly mentioned the intervention delivered and the intended population were included. The papers that did not clearly state the targeted population were excluded. For instance, the articles about bleeding caused by non-traumatic events, such as stroke, aneurysm, or damaged blood vessels due to hypertension, were eliminated. Additionally, undetermined or insufficiently strong study designs, such as editorials, case reports, conference abstracts, and letters, were all excluded from the final results. The papers that did not clearly define the intervention delivered or the settings where the intervention was utilized were excluded. Studies were considered eligible for analysis if the relevant outcomes were measured and reported, which are mortality rate, survival rate, and neurological function. Furthermore, if the targeted outcomes

from the intervention were irrelevant to patients' outcomes and did not match the inclusion criteria, such as focusing on health care providers and economic results, they were excluded. All eligibility-related screening issues were solved only by the author. Moreover, in accordance with the PRISMA statement, a flow chart by Covidence was created where the excluded studies along with the exclusion reasons were reported to demonstrate the systemic phases of the systematic review (33).

➢ 2.3 Data extraction and management

Data collection and extraction processes were carried out using Covidence software, which is a Cochrane online tool for conducting systematic reviews to ensure accuracy (34). The main findings of each study will be summarized in tables. Furthermore, EndNote 20 was used to create a database of bibliographic references. The following data were extracted from the included articles:

Population: demographic characteristics (age, gender), eligibility criteria, total number in comparison groups, withdrawals, and follow-up losses with reasons.

Intervention: number of doses, dosage, and administration method

Outcome: the aforementioned targeted outcomes, with the length of follow-up

Studies: study design, time, and duration. If trials: randomization, the method of allocation concealment, and participants' blinding (35).

➢ 2.4 Risk of bias assessment and quality assessment

The evaluation of the studies that were included required a different set of quality assessment tools to be used depending on the type of study that was conducted. For example, the Newcastle-Ottawa tool (NOS) was used for the

included observational studies by evaluating three domains, which are selection, comparability, and outcome (36). Additionally, included clinical trials were graded based on the three domains of the Jadad score, which are randomization, blinding, and accountability of all participants, including withdrawals (37).

I reviewed the appendices done by the original investigators of the included studies for any missing data and counted the number of withdrawals, dropouts, and follow-up losses for each trail. If a justification for missing data was reported, I conducted the analysis based on participants who had complete data.

3. Results

3.1 Search results

A total of 304 records were retrieved through the search process conducted until May 30, 2023: 19 papers from PubMed, 1 from Cochrane, 122 from Embase, 91 from Ovid, and 27 from Medline (Ovid). Additional studies were discovered through a reference search of those studies. 47 studies were identified for the full-text review based on their title and abstract. This systematic review includes five studies; one of them is a randomized controlled trial, and the other four are observational studies (25, 38-41). Additionally, one of the observational studies is a retrospective analysis of the included trial (41). The review involved 7503 participants with acute traumatic brain injury (TBI) of various severity from six different countries, four of which are considered high-income countries, one is upper-middle-income, and the last is a low-income country. 1635 patients received tranexamic acid (TXA) intravenously in the pre-hospital setting. 1286 of the patients received TXA as a bolus followed by infusion (maintenance), and 349 received it as a bolus of 2 g only. All included studies reported the primary outcome of this review, which is mortality incidence, either in hospitals or at one month. Furthermore, in all included studies, P-values under 0.05 (95% confidence interval [CI]) were statistically significant. Neurological function

measures were reported using different scores in the included studies, such as GOS and GCS, as well as possible complications (Table 2). The PRISMA flow chart is shown in Figure 6.

3.2 Excluded studies

47 studies were initially chosen for full-text review, and 42 did not meet the eligibility requirements and were excluded for the following reasons: inappropriate study setting (= 21), inappropriate outcomes (= 4), inappropriate intervention (= 4), inappropriate study design (= 9), inappropriate patient population (= 2), or inappropriate comparator (= 2) (Figure 6).

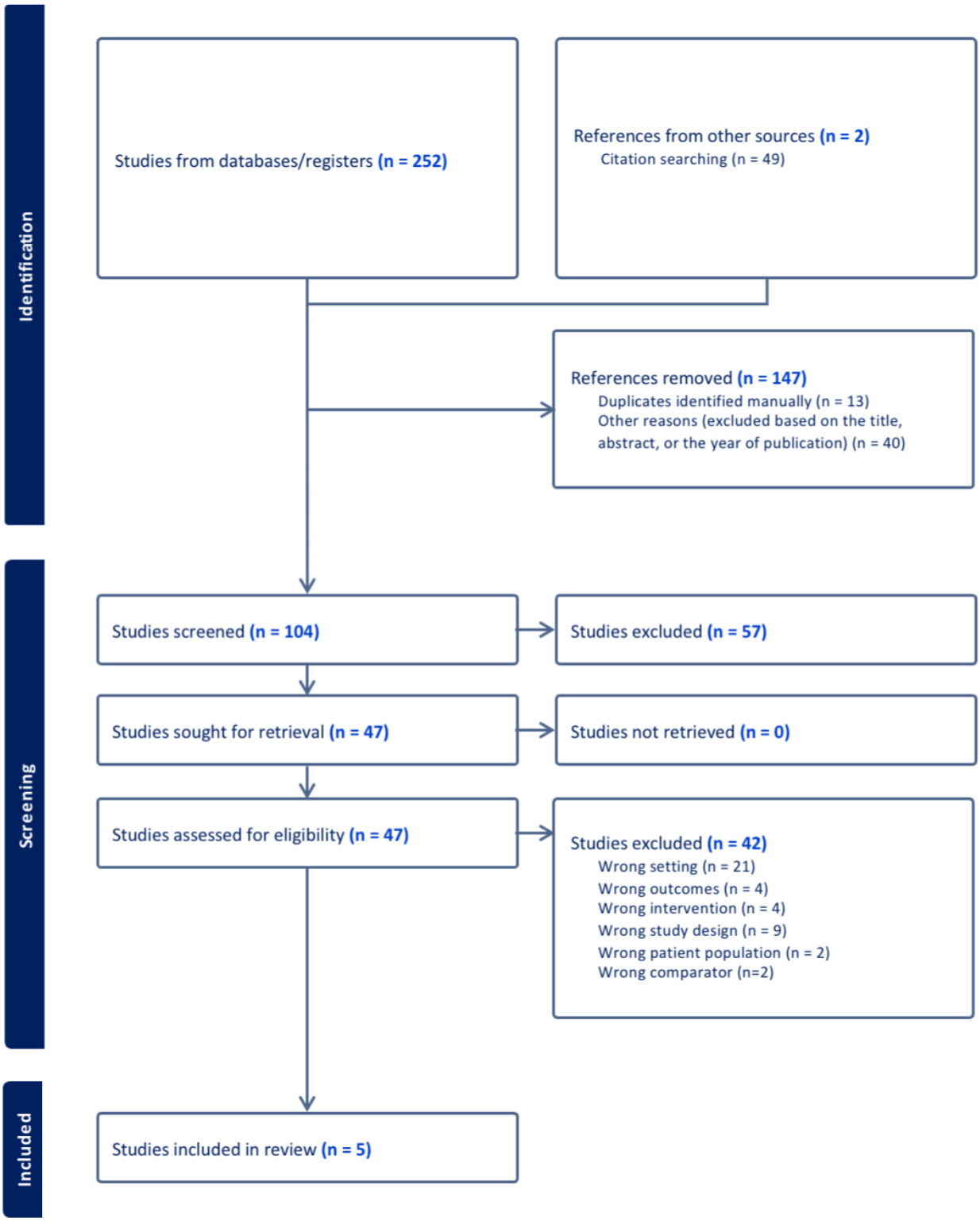


Figure 6 : PRIZMA flow chart

- **Clinical characteristics of the included studies**

Author, study	Study design	country	Number of participants	TBI severity	Dosage (g)	Study duration	Primary outcome	Secondary outcome
D. Morte et al, 2019	Retrospective review	Iraq and Afghanistan	4476 patients (174 with TXA)	Mild to severe TBI	1g IV bolus, followed by 1 g infusion/8 hours	7 years	○ Mortality in hospital ○ Neurological function at discharge	Complications
S. Bossers et al, 2020	Retrospective analysis	Netherlands	1827 patients (684 with TXA)	Severe TBI	○ 1 g bolus followed by 1 g infusion/8 hours ○ 2 g bolus ○ Less than 2g	5.10 years	○ Mortality at 1 month	Neurological function at discharge
K. Wessem et al, 2021	Retrospective analysis	Netherlands Australia United states	234 patients (120 with TXA 50%)	Severe TBI	1 g IV bolus, followed by 1 g infusion/8 hours	7.5 years	- Mortality in hospital	Complications
J. Harmer et al, 2022	Retrospective analysis	- United states - Canada	966 patients (657 with TXA)	Moderate to severe TBI	○ 1 g IV bolus, followed by 1 g infusion/8 hours ○ 2 g bolus	2 years	○ Neurological function at 6 months	○ Mortality at one month ○ Neurological function at discharge ○ Complications
S. Rowell et al, 2020	Randomized double-blind clinical trial	- United states - Canada	966 patients (657 with TXA)	Moderate to severe TBI	○ 1 g bolus followed by 1 g infusion/8 hours ○ 2 g bolus	2 years	○ Neurological function at 6 months	○ Mortality at one month ○ Neurological function at discharge ○ Complications

Table 2: Clinical features of included studies

3.3 Risk of Bias and Quality assessment

The domains evaluated for potential bias include random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting. This review includes one trail done by S. Rowell et al. with a Jadad score of 5, which indicates a high-quality trial. The risk of bias was classified as "low" in all domains except for the incomplete outcome data domain, which was deemed to have an "unclear" risk. The trial used computer-generated randomization and ensured appropriate concealment of the drug kit allocation process. The patient characteristics in both groups appeared to be similar. Furthermore, EMS agencies, patients, and people who delivered the intervention were blinded, and the intention to treat analysis was applied in the final evaluation. However, due to the loss of follow-up caused by the dropouts in the first six months, the complete data sets for the primary outcome were not available (Table 3)(25).

Author, Year	Random sequence generation	Allocation Concealment	Double-Blinding	Description of dropouts	Incomplete outcome data	Power analysis	Intention to treat	Jadad score
S. Rowell et al, 2020	L	L	L	L	U	Yes	Yes	5

Table 3: Risk of bias assessment; L = low risk, U = unclear risk, H = high risk

Author, Year	Selection				Comparability		Outcome			Total score (out of 9)
	The exposed cohort Represenativeness	*Non exposed cohort selected from the same source*	*Exposure ascertained*	*Outcome of interest was not present at the start of the study*	*Matching age and sex*	*Controlling additional confounders*	*Adequate assessment*	*Follow-up was long enough*	*Adequate Follow-up*	
D. Morte et al, 2019	1	1	1	0	1	1	1	0	0	6
S. Bossers et al, 2020	1	1	1	1	1	1	1	0	0	7
K. Wessem et al, 2021	1	1	1	1	1	1	1	0	0	7
J. Harmer et al, 2022	1	1	1	1	1	1	1	0	0	7

Table 4: Newcastle Ottawa Scale (NOS) of cohort observational studies

Regarding the assessment of observational study quality, eligible studies were evaluated using the Newcastle-Ottawa Scale (NOS). The included studies were evaluated across three broad domains: study selection (four points), study population comparability (one point), outcome of interest, exposure (in case-control studies), and

ascertainment (three points). The maximum number of stars that may be given to a study is one in either the selection, exposure, or outcome categories, and two in the comparability category. Four of the included studies are retrospective observational studies, resulting in a loss of two points in the outcome domain, which focuses on a specific aspect of the quality of case-control study designs. Therefore, a single study's overall score might be anything from 0 to 9. If a study received seven or more stars, it was deemed to be of very high quality (Table 4) (38-41).

3.4 Primary outcomes

- ***Mortality:***

Author, year	Main finding	Conclusion
D Morte et al, 2019	○ a statistically significant difference was observed with a P-value of 0.028.	○ The TXA group had a considerable decrease in mortality rates in the hospital.
S. Bossers et al, 2020 (Confounder adjustment)	*30 days:* ○ In isolated TBI, A statistically significant difference was detected with a P-value of 0.005. *12 months:* ○ A statistically significant difference was observed in cases of isolated TBI, with a p-value of 0.02.	○ The study findings indicate that there was no increased risk of death within 30 days or 12 months among the entire cohort or among those with confirmed TBI, but the risk of death was higher among those with isolated TBI.
K. Wessem et al, 2021	○ The obtained p-value of 0.45 suggests the absence of a statistically significant difference.	○ There was no difference in 30-day mortality between TBI patients who received TXA and those who did not get TXA.

J. Harmer et al, S. Rowell et al, 2022	*28-day:* ○ According to the calculated p-value, there was no statistically significant difference.	○ The results indicate that there was no significant variation in the 28-day mortality rate among patients with TBI who received either bolus or bolus maintenance of TXA and those who did not receive TXA at all.

Table 5: Main findings pertaining to mortality as reported in the included studies

All of the included studies reported the primary outcome, which is the mortality rate, for traumatic brain injury (TBI) patients who received tranexamic acid (TXA) in the prehospital setting. The death rate was calculated at different time points, which are at the hospital, during a month, and during a year. The study that reported in-hospital mortality showed that there was an improvement in mortality within TBI patients who received TXA, although patients in this group were sicker (lower GCS, higher transfusion requirements), but there was no significant difference (38). Regarding the one-month mortality rate, two studies evaluated the death rate at 30 days, and their results indicated that there was no difference in mortality in the two groups of TBI patients, whether those who received the drug or those who did not receive it (39, 40). Another trial, with a retrospective analysis of it, reported death at 28 days and showed similar findings between both groups (25, 41). Regarding mortality in a year, the results from one study revealed that there is no difference in the death rate between the TXA and placebo groups (39). However, one study found that the mortality rate was higher within either a month or a year for patients with isolated TBI who received tranexamic acid (Table 5) (39).

3.5 Secondary outcomes

- ***Functional outcomes at discharge and over a month to six months***

Author, year	Main finding	Conclusion
D. Morte et al, 2019	*At discharge:* ○ a statistically significant difference was observed with a P-value of 0.01.	○ TXA administration was linked to a substantial improvement in neurologic outcomes. Upon discharge, all patients who received TXA had a GCS of 14 or greater, which suggests either full neurologic recovery or mild TBI.
S. Bossers et al, 2020 (Confounder adjustment)	*At discharge:* ○ No statistically significant difference was found, as indicated by the calculated p-value in the adjusted analysis.	○ There is a lack of evidence indicating a correlation between exposure to TXA in patients with TBI, whether in an isolated or confirmed TBI group, and a poor neurological outcome as indicated by a low Glasgow Outcome Scale (GOS) score.
J. Harmer et al, S. Rowell et al, 2022	*At discharge:* ○ A lack of statistical significance in the DRS score is shown by the p-value of 0.29. *After six months:* ○ The calculated p-values of 0.16 (benefit) and 0.84 (harm) indicate a lack of statistical significance.	○ In either TXA therapy group, either bolus only or bolus maintenance, the good neurological results (GOSE score of 4 or below) at discharge and six months were not statistically different from placebo group outcomes.

Table 6: Main findings pertaining to functional outcomes as reported in the included studies

Regarding the functional outcomes of TBI patients who received TXA by the paramedics, four studies reported them using different measurement tools and at two different times, either at discharge or over 6 months. There are three studies that showed that there is no difference when comparing the functional outcomes at discharge of the

TXA group and the placebo group by calculating the neurological function using the GOS score, GOSE, or DRS (25, 39, 41). However, one study demonstrated an improvement in the neurological function at discharge of TBI patients who are TXA recipients, as they exhibited a GCS score of 14 or above (38). The functional outcomes of the use of TXA over six months were reported in two studies, one of which is a trial and the other is a retrospective analysis of the trial. The results showed no difference in disability or neurological recovery between the TXA group and the placebo group (Table 6) (25, 41).

- ***Complications***

Author, year	Main finding	Conclusion
D. Morte et al, 2019	The study found that there were no statistically significant differences between the TXA and non-TXA groups in relation to thromboembolic events (p-value = 0.59) and intubation at discharge events (p-value = 0.46).	○ Tranexamic acid (TXA) has been demonstrated to be a secure and efficacious medication for patients with TBI.
K. Wessem et al, 2021	○ Infectious complications had a P-value of 0.002, indicating a significant difference. ○ There was no statistically significant difference in thromboembolic events, MODS, or ARDS events.	○ The morbidity of TBI patients with and without TXA was similar. The patients who survived exhibited a prolonged stay in the ICU and a higher incidence of infectious complications.
J. Harmer et al, S. Rowell et al, 2022	○ The findings indicate that there was no significant statistical difference between the TXA and non-TXA cohorts about the incidence of complications.	○ There are some adverse events that occurred in one group more or less than the other, but none of which have a statistically significant difference.

Table 7: Main findings pertaining to possible complications as reported in the included studies.

Regarding the possible complications of the use of TXA in TBI patients in pre-hospital settings, four studies reported different numbers of adverse events that occurred to the patients after the TXA administration during their stay in the hospital. Thromboembolic events were the most frequently reported complications in all studies. Other complications were measured separately in all studies, including seizures, multiple organ dysfunction syndrome (MODS), acute respiratory distress syndrome (ARDS), and intubation at discharge. Furthermore, the results of all studies showed that there was no effect of increasing complications on the TBI patients who were given TXA over the placebo group. The incidence of complications was similar in both groups (25, 38, 41). However, one study proved that infectious complications had a high incidence in TBI patients who received TXA in contrast to TBI patients who did not receive TXA, which occurs due to the length of the ICU stay (Table 7) (40).

4. Discussion

4.1 Summary

This review is intended to investigate the effect of the administration of tranexamic acid (TXA) in the pre-hospital environment for patients with traumatic brain injury (TBI) on various patient outcomes, including mortality, functional outcomes, and medical complications. The results found that the mortality rates reported in the included studies for TBI patients who were given TXA while on the way to the hospital were different. One study demonstrated that mortality decreased in TBI patients who received TXA, although other studies found that there was no significant difference in mortality. Furthermore, one study showed that the risk of death is higher in patients who have isolated TBI. Additionally, functional outcomes were reported at discharge and over six months, and most of the studies' findings showed that there was no significant difference between TBI patients who received TXA and TBI patients who did not receive it, except one study demonstrated an enhancement in neurological function for TBI patients who received TXA. Moreover, the results indicate that the administration of TXA in the prehospital setting for TBI patients is safe in terms of the increased risk of complications.

- ***Interpretation and critical appraisal of the results***

The study by D. Morte et al. showed that the mortality rate is lower in TBI patients who received TXA in pre-hospital settings, neurological outcomes improved, and there is no difference in medical complications in the TBI patients in the TXA group (38). However, there are a number of serious limitations to this study, as it was conducted in combat settings, including the diversity of patient characteristics. For example, the TBI patients in this TXA group had higher penetrating injuries,

lower GCS, higher transfusion requirements, and higher neurological interventions. Furthermore, as it is a retrospective observational study, all of the included records were taken from documents written ten years before the study started without specific standards, incomplete records were deleted, and it was not clarified if there were other interventions that might affect the results, such as additional medication or infusion.

The study by S. Bosseres et al. demonstrated that the mortality rate is higher in patients who had isolated TBI and received TXA without any difference in the functional or neurological outcomes between TBI patients who received TXA and those who did not (39). However, although confounders were adjusted through several sensitivity analyses, unnoticed confounders and missing data can not be excluded. Additionally, the relationship between the effects of different doses has not been clearly demonstrated in the study, although the TXA doses given vary widely in the included data (39).

The study by K. Wessem et al. showed that the administration of TXA in TBI patients is not associated with mortality benefits or complications risk, except for infectious disease complications, which are caused by a long ICU stay (40). However, it is essential to clarify that the primary limitation of this retrospective analysis is the low sample size from a single center, which therefore reduces the statistical power of the study, limits generalizability, and increases the risk of bias.

The trial by A. Rowell et al. demonstrated that pre-hospital TXA administration does not have an effect on mortality, neurological outcomes, or complication incidences (25). However, in the early phase of the trial, there was a significant difference in mortality between TBI patients in the TXA group and the non-TXA group, which could potentially lead to disproportionate dropouts. Therefore, in this

trial, 15% of the follow-up was lost, compromising the trial's internal validity due to the possibility of overestimation or underestimation of the treatment effects. Moreover, a reduced sample size resulting from a 15% follow-up loss may result in a decrease in statistical power, thereby limiting the accuracy of detecting significant effects.

The study by J. Harmer et al., which was a retrospective analysis of the trial done by A. Rowell et al., evaluated the adverse events and functional outcomes using the trial's data. The results showed the same results as the trial: there is no difference in the occurrence of complications in one group over the other (41). However, this retrospective analysis was not predetermined at the time of the trial, and it was started two years after

the trial publication date. Therefore, the data about complications and adverse events associated with the use of TXA for TBI in pre-hospital settings were not preserved and collected based on standardized protocols.

Moreover, three of the five studies included in this review had inadequate sample sizes. The presence of limitations and weaknesses may have introduced bias into the review's findings. However, although there are various limitations in the included studies, this systematic review represents the first-ever comprehensive analysis that provides a complete summary of every single study conducted in pre-hospital settings.

4.2 Previous studies findings

The CRASH-3 trial is the most recent trial related to the area of my research, as it focused on the administration of TXA for TBI patients. However, the administration of the TXA in the CRASH-3 trial was in the ED, not in the pre-

hospital setting. Therefore, it was excluded from the analysis. Furthermore, the death-related outcomes of the trial and my systematic review were similar in the severe TBI population. In contrast, patients with mild to moderate TBI showed a lower mortality rate after the administration of TXA in the CRASH-3 trial (24).

A previous meta-analysis published in 2020 by H. Chen et al. assessed the efficacy of the administration of tranexamic acid for TBI patients using data from published RCTs up to August 2018. The mortality rate was the primary outcome of the study, and unfavorable neurological outcomes, the progression of the hemorrhagic mass, neurological interventions, and complications, such as thromboembolic events, were the secondary outcomes. Four studies in this meta-analysis reported mortality rates and showed a significant decrease in the death rate in TBI patients who received TXA. Regarding the secondary outcomes, the meta-analysis findings demonstrated similar results between both TBI groups, except for the progression of hemorrhagic mass, which was reduced in TBI patients who received TXA (42).

Another previous meta-analysis and systematic review by J. July et al. evaluated the efficacy and safety of the administration of TXA in TBI patients. The primary outcomes were mortality rate, the progression of the hemorrhagic mass, neurological intervention, and unfavorable GOS, and the secondary outcomes were thromboembolic events and vascular occlusion. The meta-analysis findings showed a decrease in mortality rate in the TBI patients who received TXA. Furthermore, the risk of complications, functional outcomes, and neurological interventions were similar in both TBI groups, whether they received TXA or not. However, the hemorrhagic mass expansion was reduced in TBI patients who received TXA (43).

Both previous published meta-analyses showed similar findings in terms of reducing mortality and the similarity in the effects between TBI patients in the TXA group and the placebo group on functional outcomes and the risk of complications. Furthermore, they share some limitations. In most of the included RCTs, the average time from the insult to the administration of the TXA was only reported in a small number of trials. Additionally, the methods of TXA administration were different, and the effect of different methods was never measured in both meta-analyses. Therefore, it is not possible to conduct a dose-response analysis. Moreover, both have potential publication bias risks due to the small sample size of the few included RCTs in each meta-analysis (42, 43).

According to my systematic review, the overall patterns showed that the use of TXA in pre-hospital settings for TBI patients had no mortality risks compared to TBI patients without TXA, except in isolated TBI, in which the use of TXA in the pre-hospital environment could increase the risk of death. However, the results of previous meta-analyses were different from the results of my systematic review. As they demonstrated a decreased mortality rate in TBI patients who received TXA. Furthermore, the findings of this systematic review and the previous meta-analyses in terms of secondary outcomes showed similar findings. Moreover, when comparing the findings in my systematic review and the previous meta-analyses, several factors may affect the outcomes (42, 43). One of the contributing factors is time. The results of my systematic review are based on data collected in 2018, which represents the end of the data collection period for the previous meta-analyses. Furthermore, due to the lack of large-scale clinical trials since 2019, the included studies in my systematic review mainly consist of observational studies. In contrast, the previous meta-analyses included six clinical trials in each, which provided greater control over the variables used to measure the outcome. Finally, it

is important to note that this systematic review exclusively concentrated on the administration of TXA in TBI patients in the pre-hospital setting, unlike both meta-analyses, which mainly evaluated the effect of TXA in TBI patients during the first three hours of the injury, which means that the administration of TXA is not necessary to be in pre-hospital settings.

- **Prospective pre-hospital clinical trial**

A large multi-center pre-hospital randomized controlled trial known as the PATCH-trauma trial by B. Mitra et al. is exploring the effect of the TXA in pre-hospital trauma patients who are at risk of traumatic coagulopathy. The trial is running nowadays, and it aims to recruit 1316 patients from Australia, New Zealand, and Germany. The primary outcome is the functional outcome based on GOSE at six months, and the secondary outcomes are mortality rate, blood transfusion requirements, and the incidence of adverse events. Furthermore, the anticipated findings of the PATCH-trauma trial include a subgroup analysis for patients with TBI. However, at present, only the trial's protocol and the analysis plan have been published in 2021, and none of the results have been reported yet (44).

- **TXA and the progression of the cerebral hemorrhage**

A trial published in 2020 by F. Mojalla et al. assessed the effect of the emergency department (ED) administration of TXA on the prevention of cerebral hemorrhage progression in TBI patients within less than 8 hours of injury occurrence. This is a randomized, double-blinded trial containing 100 participants recruited from 2014 to 2015. The primary outcome was the progress of cerebral hemorrhage in TBI patients who received TXA in the ED by calculating the width, length, and number of slices of cerebral hemorrhage in a CT scan at the time of hospital admission and

after 24 hours. Secondary outcomes were mortality during the 7-day period and the length of the ICU stay. The study findings showed that there is no significant difference in the progression of the hemorrhagic mass in both TBI groups, either with or without the TXA. Furthermore, the results demonstrated no significant difference in the mortality rate between the TXA and placebo groups, but there was a significant difference in the ICU stay duration since the TXA group of TBI patients had shorter average hospital stays (45). The findings of this trial in terms of mortality were similar to the findings of my systematic review. However, it was not included due to the fact that it was conducted in a hospital setting.

- **The TXA administration methods**

Aside from the included studies, a cross-sectional study was done by M. Bivens et al. to clarify the consequences of different TXA administration strategies in trauma patients on mortality. This study used two databases to determine avoidable mortality related to three methods of administration of TXA, either in hospital or pre-hospital settings. Trauma-related death reports were obtained from 2007 to 2012 using Centers for Disease Control (CDC) death certificates for patients who arrived at the hospital by ambulance after obtaining approval. The risk of death reduction in the study was estimated from the CRASH-2 trial, and the statistical analysis was done using electronic software. The study included a total of 126,608 deaths. The results showed that if TXA had been administered within the first hour, approximately 3409 (2.69%) deaths due to traumatic injury by bleeding could have been prevented annually. Additionally, if TXA had been administered within the first two to three hours after the injury, it could have potentially prevented 2237 (1.76%) deaths annually. Moreover, the administration of TXA within the first hour strictly to patients with hypertension or tachycardia could potentially prevent 1371 (1.08%) deaths annually. In other words, if the TXA administration had been

started early by paramedics, 3409 annual deaths may have been avoided. Furthermore, other scenarios of TXA administration, including delayed administration or restricted administration to hypertensive or tachycardia patients, yielded a lower number of lives saved (46). However, generalizability is limited due to the fact that the findings were based solely on data from the USA trauma registry. Additionally, using CDC certificates to determine the presence of trauma-related deaths is based on the assumption that all deaths were traumatic. There is an additional source of possible bias since 50% of patients' reports were missing from the EMS field documentation. Finally, differences in TXA treatment methods, such as dosing, might lead to inconsistent outcomes.

4.3 Recommendations

The findings of this systematic review have significant practical implications for both routine practice and future research projects. Based on the available evidence, it is recommended that healthcare providers, especially emergency responders such as paramedics and ED physicians, consider the utilization of the TXA in the management of exaggerated hemorrhage due to trauma with caution in isolated head injuries. It is important to note that the available studies did not sufficiently examine the effect of different doses of TXA administration on patient outcomes (47). Most of the studies relied on the typical and common dose in the results, which is 1 gram of TXA over 10 minutes followed by 1 gram IV infusion over 8 hours, while ignoring the analysis of effects in a few groups that were given different doses, such as 2 g of TXA or less than 1 gram. Therefore, additional research is necessary to address the current knowledge gaps and establish more comprehensive evidence regarding the administration of TXA at different dosages. Moreover, there is a lack of randomized controlled trials conducted in pre-hospital settings assessing the effect of the TXA on various patient groups, such as TBI

patients and elderly trauma patients. Furthermore, most of the published studies evaluating the effects of TXA on patients did not address specific patient populations, such as patients with extreme ages or patients with high-risk thromboembolic events (48). This indicates the need for further clinical trials incorporating better control of the dosage and time in the pre-hospital field to evaluate the efficacy of the TXA in different patient groups.

4.4 Limitations

This review presents an overview of the evidence in a narrative synthesis without conducting statistical analysis regarding the effect of the administration of tranexamic acid on patients with acute traumatic brain injury. However, there are a number of limitations to this systematic review. First, this systematic review was conducted as a part of a master's degree dissertation and was completed within a three-month time frame. This time limitation may result in incomplete search processes, inaccurate data collection, and a restricted depth of data analysis, which have an impact on the overall quality and reliability of the review (49).
Second, as a result of the short time frame in which this review was written, only papers that were published within the previous five years were considered to be included. This will lead to a number of limitations, including an incomplete evidence base, restricted generalizability, excluding relevant older studies, insufficient assessment of long-term effects, and potential publication bias (50).

Third, as a result of the lack of pre-hospital clinical trials, observational studies were included in this systematic review, which resulted in a few limitations. To begin with, there are limitations related to the small number of trials, which reduce the statistical power and accuracy of the review, as the findings may have been based on a small sample size, which leads to broader confidence intervals. Additionally, observational studies rely on observations and evaluation of naturally

occurring events, and they are more subject to bias. Therefore, this review is exposed to potential confounding factors that may affect the overall validity and reliability of the results.

Furthermore, methodological heterogeneity is introduced with the combination of RCTs and observational studies. Variations in study designs, demographic features, and potential bias among the two study designs can complicate the integration of the findings and restrict the capacity to formulate a strong conclusion (51). The quality of the included studies may also vary. Although trails typically follow strict methodologies and standards, the consistency of observational studies can vary, which can introduce further ambiguity and potentially influence the overall conclusion. Moreover, establishing the causality and generalizability of the review's findings can be challenging due to the limited number of trials and the presence of confounding factors (52).

Finally, this systematic review was conducted by a single author, which makes it prone to several biases. The most significant one is the likelihood of research selection bias, as personal preferences may affect which studies are included or excluded. Moreover, as mentioned previously, the workload and time constraints make it difficult for one person to manage, which results in a narrower search area and insufficient data extraction.

Additionally, the absence of the collaboration and peer review provided by multiple authors can affect the reliability of the review, as it is more prone to mistakes, such as oversights and data extraction, analysis, and interpretation errors, which affect the comprehensiveness and depth of the review due to the limited expertise and perspective. Furthermore, the lack of varied views in interpreting and

synthesizing the findings may have an effect on the robustness and correctness of the drawn conclusion of the systematic review (53).

5. Conclusion

This systematic review has combined the existing evidence concerning the impact of the administration of TXA in pre-hospital settings for traumatic brain injury patients within the first hour of the injury in order to offer an in-depth overview of the present state of knowledge. The review has identified a total of five studies, one of which is a randomized controlled trial, and the others are retrospective observational studies. The findings of the included studies were analyzed to solve the research question. The findings of this review showed that the use of TXA for TBI patients in pre-hospital settings does not result in mortality benefits compared to not administering it. However, the risk of death increases if TXA is administered to patients with isolated TBI in pre-hospital settings. Furthermore, the administration of TXA in pre-hospital settings is not associated with increased complication risks or any neurological or functional effects, either harmful or beneficial.

The previously mentioned results contribute to the current body of knowledge regarding the use of TXA in the pre-hospital setting for TBI patients and hold significant implications for patient care, decision-making, and upcoming investigations in the pre-hospital field. It is important to recognize the limitations of this systematic review, including the short time frame for completion, the concentration on recent publications, the reliance on observational studies, methodological heterogeneity, different quality levels, and potential biases resulting from a single-author approach. It is essential to take into account these limitations while interpreting the outcomes and implementing them in real-life circumstances.

In summary, this systematic review presents significant findings regarding the use of TXA for TBI patients in the pre-hospital environment and provides recommendations for healthcare practitioners and researchers. Based on the evidence produced, this systematic review suggests a cautious consideration of the use of TXA in the management of TBI patients, particularly in cases of isolated TBI. Further research is required to investigate the effect of various dosages of TXA on various patient populations. The findings of this review can be used to guide future research in pre-hospital settings.

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