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Tranexamic acid for traumatic brain injury? The old drug raises new debate

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Abstract

Traumatic brain injury (TBI) is one of the leading causes of death and disability in children and young adults, but also an important medical problem concerning the older part of the population. TBI has an inauspicious prognosis and the mortality remains high, reaching up to 40% in severe injuries. Extensive research on treatment options that could minimize the mortality rate and the number of complications is ongoing and one of these options is tranexamic acid. One of the pathomechanisms of uncontrollable bleeding is hyperfibrinolysis, where the mechanisms controlling fibrinolysis are disrupted and cause it to become excessively intensified. Tranexamic acid (TXA) is an inhibitor of plasminogen and thus inhibits fibrinolysis. This paper aims to provide an overview of the current state of knowledge about tranexamic acid in traumatic brain injury. According to available, data pre-hospital intravenous tranexamic acid infusion administered early, within 3 hours from the injury, seems to reduce mortality in patients with mild to moderate traumatic brain injury, but in patients with severe TBI, this treatment could be associated with increased mortality. The use of TXA does not increase the risk of adverse events. Moreover, the safety of tranexamic acid has been confirmed and no correlation between the use of TXA and a higher incidence of thromboembolic events has been found. Current findings do not give a conclusive answer on the effectiveness of TXA in TBI. Large, international randomized clinical trials have to be performed to answer this question. Additionally, further studies in the use of TXA in TBI in the pediatric population are also needed.

Key words: tranexamic acid, traumatic brain injury, bleeding, brain injuries, intracranial haemorrhage, hyperfibrinolysis

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Introduction

The aim of the article

This article aims to provide an integrated overview of the current state of knowledge about tranexamic acid in traumatic brain injury, with particular attention devoted to the underlying pathomechanism of coagulopathy in traumatic brain injury (TBI), tranexamic acid (TXA) mechanism of action, and its impact on the mortality as well as a potential risk of adverse effects.

Epidemiology of traumatic brain injury

Traumatic brain injury is one of the leading causes of death and disability in children and young adults, but also an important medical problem

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concerning the older part of the population. It is estimated that sixty-nine million people worldwide suffer from traumatic brain injury every year [1]. The clinical severity of TBI is classified by Glasgow Coma Scale (GCS) scores into three categories: mild (GCS 14–15), moderate (GCS 9–13) and severe (GCS 3–8) [1]. Worldwide mild TBI occurs in 81.02% of cases, moderate TBI in 11.04% and severe TBI in 7.95% [1]. The mortality in TBI is generally high and GCS scores are good and widely used prognostic factors for mortality due to TBI. In TBI general mortality rate is about 7.8%, but it dramatically grows in severe TBI, where the mortality rate is about 30–40% and in 60% of cases mental, physical or social deficits occur [2, 3]. According to the epidemiological data from Europe the main age is between 22–49 years of age, but there are two groups in which prevalence of TBI is higher, under 25 years old and over 75 years old. More patients are male. The most frequent mechanisms of injury are falls and road traffic accidents [4].

Pathophysiology

Traumatic brain injury is a complex disorder with complicated pathophysiology that varies depending on the severity of injury, mechanism and individual coexisting physical conditions. Direct damage of the brain, functional changes, metabolic disturbance, reduction in cerebrospinal fluid flow, diffuse axonal injury, excitotoxicity, ionic flux, inflammation and complex form of vascular disruption including subdural and epidural hematomas, haemorrhagic lesions within the cortex, coagulopathy and functional changes in endothelial cells play a direct role in the pathology of TBI [2, 5]. Understanding the underlying mechanisms of TBI is crucial for the development and application of a treatment strategy.

Intracranial bleeding is one of the results of TBI and tranexamic acid can play a role in the management of that pathology. Intracranial bleeding and cerebral oedema lead to elevation of intracranial pressure, which results in reduced cerebrospinal fluid perfusion, higher risk of ischaemia and potentially life-threatening brain herniation [2]. This mechanism is well known, but bleeding in TBI does not result only in elevation of intracranial pressure, but leads to various pathophysiological dysfunctions like local oedema, ischemia and consequently tissue damage, neuron necrosis, inflammation and gliosis [5]. Bleeding in TBI is not only a result of the mechanical damage to blood vessels during injury, but also coagulation abnormalities and dysfunction of endothelial cells are underlying causes. A meta-analysis of 34 studies has shown that in 32,7% of TBI coagulopathy was present. Moreover, coagulopathy was related to higher mortality and unfavourable outcome [6]. In one study, the overall hospital mortality for patients with isolated blunt TBI with coagulopathy was 50,4% as compared to 17.3% for patients without coagulopathy [7]. Many studies confirmed the presence of coagulation abnormalities in patients with TBI, but due to different criteria of coagulopathy in each of these studies, it is complicated to compare the results and describe specific types of present coagulation abnormalities [6]. Coagulation disorders in TBI are a complex combination of hypercoagulability and coagulopathy. Hypercoagulability is the increased tendency to formation of fibrin in blood vessels, both generalised in case of disseminated intravascular coagulation (DIC) or local leading to the formation of microthrombi in the penumbra of the brain injury [6]. Some studies have shown that brain tissue is highly rich in many procoagulant molecules, but the role of that fact in the development of coagulation abnormalities in TBI is unknown [8]. The cause of brain trauma-associated coagulopathy is multifactorial and includes consumption of platelets and coagulation factors as well as dilution during fluid resuscitation [8]. Not only resources of clotting factors play a role in the haemostasis, but also proper function and regulation of coagulation cascade and fibrinolysis. In trauma patients, disturbance in physiology can leads to the development of a lethal triad including a vicious cycle of coagulopathy, hypothermia and acidosis [8]. One of the possible coagulopathies in TBI is hyperfibrinolysis, which is a result of tissue injury in which the endothelium of the vessels is damaged and the plasminogen activator is excessively released. This leads to a systemic, not only local as it usually occurs, excessive fibrinolysis and failure in inhibiting mechanisms [9]. The presence of hyperfibrinolysis in patients with TBI is one of the theoretical bases of the usefulness of TXA in that group of patients.

Pharmacology of tranexamic acid

Tranexamic acid is a well-known drug widely used in various areas in medicine. The mechanism of TXA action is to bind to the lysine-binding site of plasminogen and inhibit its ability to bind fibrin which decreases fibrin degradation. This leads to the stabilisation of the thrombus and through that improves haemostasis. During vascular injury, subendothelial matrix proteins are exposed and released which initiates coagulation cascade, but

among these proteins are also plasminogen activators [10]. Physiologically coagulation cascade is more effective than fibrinolysis and formation of the thrombus is possible. In TBI, other trauma injuries and during large operations this physiological balance can be disturbed by excessive plasminogen activators release, ineffective mechanisms of regulation and inhibition of fibrinolysis, which finally leads to systemic, not only local, fibrinolysis and pathological response to the injury known as the hyperfibrinolysis [9, 11, 12]. Hyperfibrinolysis is one of the pathomechanisms explaining why TXA can be an effective drug during traumatic brain injury. TXA can be administered both orally and parenterally, but in TBI intravenous administration is preferred. Intravenous administration of a 1g dose corresponds with a plasma concentration of about 10 mg/L which is achieved for 5–6 hours [13]. The therapeutic plasma concentration of TXA is unknown and varies from 5 mg/L to 15 mg/L in different studies [13–15]. The half-life of TXA is about 2–3 hours [13]. TXA crosses the blood-brain barrier [13]. Elimination is in an unchanged form by kidneys, after administration of 10 mg/kg body weight of TXA, 90% was recovered in the urine within 24 hours [11, 13, 16].

Use of tranexamic acid in traumatic brain injury — recent studies and the current debate

Clinical randomisation of an antifibrinolytic in significant head injury-3 (CRASH-3)

In 2019 "The Lancet" published results of the international multi-centre large randomised placebo-controlled clinical trial entitled Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury Clinical randomisation of an antifibrinolytic in significant head injury-3 (CRASH-3), which was done in 175 hospitals in 29 countries and the total number of enrolled patients, who were treated within first 3 hours, was 9202 [17]. Adult patients with TBI, who had a GCS score of 12 or lower or any intracranial bleeding on CT scan and no major extracranial bleeding were eligible. After randomisation patients receive an intravenously loading dose of 1 g of TXA infused in 10 min and then 1 g by infusion over 8 hours or placebo 0.9% sodium chloride according to the same protocol. The time window for eligibility was originally 8 hours, but due to external evidence that TXA administered after 3 hours of injury is probably ineffective, the time window was shortened to 3 hours [17].

The primary outcome was head injury-related death within 28 days of injury. The results have shown that the risk of head injury-related death was 18.5% in the tranexamic acid group versus 19.08% in the placebo group [relative risk (RR) 0.94], but when patients with a GCS score of 3 or bilateral unreactive pupils at baseline were excluded from the analysis the risk of death was 12.5% in the TXA group and 14.0% in the placebo group (RR 0.89). The risk of heat-related death with TXA after stratification by baseline GCS and pupillary reactions was lower in patients with mild to a moderate head injury (GCS score 9–15, RR 0.78), but not in the patient with severe TBI (GCS score 3–8, RR 0.99). In a regression analysis patients with reactive pupils in comparison with patients with unreactive pupils had a lower risk of head injury-related death with TXA (RR 0.87). The authors examined the effect of TXA on head injury-related death stratified by time and early treatment reduced risk of death in mild to moderate injury, but not in patients with severe TBI. Disability measured by Disability Rating Scale score and an outcome measure designed by patient representatives was similar with TXA and placebo group.

The risk of thromboembolic events and other adverse effects was similar in the tranexamic acid and placebo groups. Also, the risk of seizures was similar between groups.

CRASH-3 trial was a continuation of previous RTCs conducted worldwide to evaluate the use of corticosteroids in traumatic brain injury (MRC CRASH trial) and the use of TXA in trauma injury (CRASH-2 trial) [18, 19]. MRC CRASH trial has provided evidence that administration of methylprednisolone in TBI does not reduce the risk of death within 2 weeks since injury [19]. Clinically significant results of the CRASH-2 trial were published in 2013 by Roberts et al. [20] and has shown that early TXA administration in bleeding trauma injuries reduces all-cause mortality and also mortality due to bleeding, without increased risk of adverse events compare to the placebo group. Since that publication TXA administration appear in many traumatic injury protocols worldwide, however, the safety and efficacy of TXA remained uncertain. Many concerns were raised by the results of studies on the use of TXA in aneurysmal subarachnoid haemorrhage, which have shown that the drug reduced the risk of re-bleeding, but without the improvement of the clinical condition of patients and reduced mortality. That treatment in five studies was associated with an increased risk of cerebral ischaemia [21]. That result has

Table 1. The most important conclusions from multicentre randomized clinical trials are shown, as well as the meta-analyses covering the latest results of clinical trials

Author, year [ref.]	Study type	Number of patients	Main conclusions
Lawati, 2021 [25]	Meta-analysis	14,747	TXA probably does not affect mortality or risk of disability
Bossers, 2021 [23]	Multisite RCT	1,827	TXA administration was associated with increased mortality in patients with isolated severe TBI
Rowell, 2020 [24]	Multisite RCT	966	TXA does not affect mortality or risk of disability
Yokobori, 2020 [26]	Meta-analysis	10,044	TXA reduced the risk of head injury-related death
Roberts, 2019, CRASH-3 [17]	Multisite RCT	12,737	TXA reduced the risk of head injury-related death in patients with a mild-to-moderate head injury, but not in patients with a severe head injury
Perel, 2012, CRASH-2 IBS [22]	Multisite RCT	270	TXA was likely to be associated with a reduction in haemorrhage growth, fewer focal ischaemic lesions, and lower mortality

RCT — randomised controlled trial; TXA — tranexamic acid

raised many concerns among clinicians regarding the safety of TXA administration in intracranial bleeding. Inconclusive results and clinical needs for improvement TBI treatment were an inspiration for the CRASH-2 Intracranial Bleeding Study, a part of the CRASH-2 trial, in which a subgroup to quantify the safety and effectiveness of TXA on intracranial haemorrhage in patients with traumatic brain injury was created [22]. In the results published in 2011, there was moderate evidence that early TXA administration can reduce haemorrhage growth and mortality, without increased risk of ischemia [22]. The promising conclusion of that trial provides grounds for further clinical trials evaluating the effect of tranexamic acid in patients with traumatic brain injury and finally leads to design and conducting the largest RCT in that population, CRASH-3 trial described above. The safety was confirmed, but efficiency remained questionable.

In another large multicentre, cohort clinical trial recently published in "JAMA Neurology" by Bossers et al. [23] including 1827 patients the results contradict positive and promising conclusions of the CRASH-3 study and previous pilot trials. TXA was given prehospitally only to patients with clinically suspected severe TBI (GCS score 8 or less) and primary outcome. The primary outcome was 30-day mortality. The results were negative and had shown that in the TXA group compared to placebo mortality was higher [odds ratio (OR) 1.34, $p < 0.01$] compared with the group without TXA administration. That result was observed in the entire cohort, but analysis showed that in patients with isolated severe TBI without extracranial bleeding 30-day mortality was even higher than in the entire cohort (OR, 4.49, $p = 0.005$). Moreover, for the secondary outcomes, the analysis showed higher 12-month mortality, lower GCS score at discharge and longer hospital length of stay in the case of patients who received TXA [23].

The importance of the CRASH-3 study is visible in the publication of the study by Rowell et al. in 2020 in "JAMA" [24]. They assess the effect of pre-hospital TXA administration on 6-month neurological outcome and mortality in patients with moderate and severe TBI. It is not without significance that the authors completed the trial long before the publication of the CRASH-3 trial but decided to publish results after the publication of the CRASH-3 trial, which is a form of publication bias. The pre-hospital treatment was initiated within 2 hours of injury as 1 g intravenous bolus of TXA and then continued in hospital as an 8-hour infusion of the same dose, the placebo group received placebo in the same regimen. The results showed that there was no difference in 28-day mortality between groups, 6-month Disability Rating Scale (DRS) score as well as the progression of intracranial haemorrhage.

The authors mentioned above discussed all large RCTs published in recent years. There is a visibly growing number of large RCTs completed recently, but still, further studies are needed. Due to a small number of patients and low strength of evidence the rest of the RCTs were not mentioned in this article, but the summary is available in Table 1 [17, 22–26], and the results are analysed and discussed below in review articles and meta-analyses [27–32].

Meta-analyses of randomised clinical trials — questionable effectiveness of tranexamic acid

The latest meta-analysis including nine recent randomised control trials (RCTs), among others, the CRASH-3 study, but in addition to the Bossers's publication, Lawati et al. in 2020 in "Intensive Care Medicine" was published as well [25]. The most significant conclusion of this study is that tranexamic acid does not reduce mortality and disability measured by DRS. TXA administration reduces hematoma expansion measured in millimetres on subsequent neuroimaging, but this result is of a rather limited clinical significance. Moreover, there is no evidence, that use of TXA was associated with shorter hospital stay or shorter Intensive Care Unit stay and with reduced need for neurosurgical interventions. This study confirmed the safety of TXA use in TBI and in the TXA group the risk of deep vein thrombosis, vascular occlusive events, stroke or seizures was not increased in comparison with the placebo group.

Yokobori et al. [26] included studies up to 2019 (a total of seven studies) in their meta-analysis. The authors concluded that there was no difference between the TXA group and placebo group in mortality, neurological outcome and adverse effect, including ischemic or thromboembolic events. The weakness of this publication is a lack of analysis of two large RCTs published by Bossers et al. [23] and Rowell et al. [24], which is justified by their subsequent publication but still influence the results. The rest of the previously published meta-analyses encountered the same problem therefore new analysis including all recently published RCTs is needed.

Discussion

Since the publication of the results of the CRUSH-3 trial, a new lively debate has begun, but the clinically significant question if tranexamic acid use is effective in TBI is still hard to answer. The largest ever published RCTs covering that topic, CRASH-3, did not give similarly strong evidence for benefits of TXA administration to patients with trauma injury as the CRASH-2 study. Despite that CRUSH-3 trial provides significant conclusions. The study confirmed the safety of TXA administration to patients with TBI and the strongest concerns of increased risk of ischemia were not confirmed. Moreover, this study by subgroup analysis divided patients into groups, who can or cannot, benefit from TXA administration. Currently available data from the CRUSH-3 trial suggests that TXA administration to patients with severe TBI (GCS score 8 or less) does not reduce mortality, but in the case of patients with mild to moderate TBI, it does [17]. Furthermore, a study published by Bossers et al. [23] gave evidence that pre-hospital TXA administration was associated with higher mortality in the case of patients with severe TBI, especially isolated TBI. Bossers's publication was not included in any systematic reviews and meta-analysis mentioned in that publication, therefore future analysis taking that publication into account can provide results showing that TXA use is even less efficient. In future meta-analyses, a cohort analysis will be relevant, because Bossers et al. [23] only investigated patients with severe TBI. These results challenge TXA infusions in patients with trauma injuries including TBI. The possible explanation of the ineffectiveness of TXA administration in patients with severe TBI is that in more severe TBI the physical destruction of large vessels is more important than secondary coagulopathy and dysfunction of small vessels, in which cases TXA can be helpful due to its mechanism of action [8]. Rowell et al. [24] had a shorter window for initiation of the treatment in their trial because the TXA was administered within 2 hours from the injury while in other studies that window varies from 3 to 8 hours. Despite the early beginning of treatment, the results did not confirm the effectiveness of TXA [24]. There is evidence that TXA should be infused as soon as possible and the beginning of treatment after 3 hours from the injury seems to be ineffective, which was the reason for a change in CRASH-3 trial protocol limiting recurvation to patients within 3 hours from the injury. In the majority of cases, the first dose of TXA is followed by 1 g infusion while 8 hours, which is a complication for emergency teams, but the result from surgical studies provides evidence that high-dose bolus of TXA increased the risk of seizures without better control of bleeding [33]. The effect of TXA on the progression of intracranial haemorrhage is also widely discussed and present in many study protocols, but progression assessment requires subsequent neuroimaging and most importantly should correlate with the clinically significant outcomes like mortality or need for neurosurgical intervention. In the CRASH-2 Intracranial Bleeding Study TXA administration seems to reduce haemorrhage growth, but the clinical importance of that result was uncertain. Rowell et al. did not confirm the reduction of progression in intracranial haemorrhage in a patient receiving TXA. Currently, available meta-analysis does not confirm the effectiveness of TXA use in

TBI, but any of the available meta-analyses include all recently published RCTs. Moreover, included in the analysis are low-quality single centre trials like in Lawati et al. [25] publication, in which 6 out of 9 trials were single centre. Analysis and interpretation of the results are complicated due to differences between trials' protocols, population, a window for randomization, assessed outcomes and the follow-up. The results of current studies do not provide a definitive answer to whether the use of tranexamic acid reduces mortality and the complication rate or not. Further studies are needed to answer that question. Moreover, the number of studies of TXA administration in TBI in children is limited and there is a need for multicentre RCTs to investigate that topic.

Conclusions

According to available data pre-hospital intravenous tranexamic acid infusion administered early, within 3 hours from the injury, seems to reduce mortality in patients with mild to moderate traumatic brain injury, but in patients with severe TBI, this treatment could be associated with increased mortality. The use of TXA does not increase the risk of adverse events.

Conflict of interests

The authors have no conflicts of interest to declare. All co-authors have seen and agree with the contents of the manuscript and there is no financial interest to report.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

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