The Potential Role of TXA in Treating Brain Hemorrhage

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Elijah Byrd graduated from Wright State University in 2023 with a BA in biological sciences. His focus is on emergency medicine. He recently moved to Columbus to pursue work at MedFlight.

Author notes:
My mom suffered a hemorrhagic stroke at the age of 52. Watching her struggle with such a life-changing event is what motivated me to study stroke and the cutting edge science behind its cure. As one of the leading causes of death and disability around the world, stroke is a problem that demands to be addressed. Although current treatment options have come a long way in recent years, there is still so much more to be discovered.

Faculty note:
Elijah reviewed the scientific literature on the efficacy of using tranexamic acid to treat a brain bleed, a deadly condition that requires rapid intervention to save the patient’s life. Tranexamic acid is widely used to treat excessive bleeding in many circumstances, but not for brain bleeds. The use of tranexamic acid is complicated by the difficulty in determining whether stroke symptoms are caused by a brain bleed, where its administration would be helpful, or a blood clot, where the drug would be detrimental. Elijah’s interest in the topic is very personal, stemming from his recent experience with his mother’s stroke. He did a great job of critically reviewing the evidence from multiple studies, and he created accessible figures to communicate the potential of this treatment to a wide audience.
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Introduction

Stroke is a dangerous, time-sensitive condition that impacts millions of people every year, becoming fatal for hundreds of thousands, and permanently disabling for even more (Guo et al. 2021). Stroke is broadly categorized into two main types: ischemic and hemorrhagic. Hemorrhagic stroke causes active bleeding in the brain and is significantly more deadly than ischemic (Figure 1). Brain hemorrhage remains fatal and commonplace, even in areas with advanced healthcare systems. Many people suffering from this serious medical emergency will die either as a direct result of destruction of their brain tissue or from one of the many complications that can arise during the long and complex treatment period following diagnosis. Even after the danger has passed, these patients will continue to struggle to lead normal lives, as stroke remains one of the leading causes of disability around the world (Liu et al. 2021).

In recent years, the quality of care for ischemic stroke patients has made great advancements. Tissue-type plasminogen activator (tPA) is a fast acting, easy to use, and relatively inexpensive drug that has proven clinically effective at curing brain ischemia (Gravanis, Tsirka 2008). tPA, colloquially known as a clot buster, works by quickly dissolving blockages during an ischemic stroke. However, due to the fundamental difference in pathology between ischemic and hemorrhagic strokes, tPA has no effect on and is contraindicated for those with intracerebral hemorrhage. This has left hemorrhagic stroke care lagging far behind the treatment options for ischemia (Sprigg et al. 2018). Until a similarly effective and efficient drug is found for treating brain hemorrhage, those suffering from it will continue to struggle against a disease that is extremely difficult to manage and cure. Tranexamic acid (TXA) has been proposed as a potential solution to this problem.

TXA is an intriguing option because much like its ischemic stroke counterpart, TXA is cheap, readily available, has quick response time, and consists of nothing more than a simple injection. Where it differs from tPA though is in its mechanism of action. TXA is essentially the opposite of tPA; it helps prevent clot breakdown, which is why it may be helpful for stroke patients whose illness is caused by active bleeding.

Early, promising evidence supporting tranexamic acid in this new role came from the CRASH-3 (Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage, third iteration) trial. This study, performed from 2012-2019, examined thousands of patients experiencing intracerebral bleeding and monitored the effects of TXA relative to a placebo. The authors of the CRASH-3 trial have championed the use of TXA for ICH after they found it significantly reduced chance of death in patients with brain hemorrhage. Several subsequent clinical trials attempting to produce similar results have instead found conflicting data, raising questions about TXA’s effectiveness and safety.

This review will examine the pathology of stroke and the function of TXA, and why the drug could be a sorely needed cure for one of the world’s most destructive diseases. I will address the differences between ischemic and hemorrhagic strokes and why a novel approach is needed to treat cerebrovascular accidents, despite the widespread effectiveness of drugs like tPA. I will break down the structure, mechanism, effects, and side effects of TXA. I will analyze critically various
studies and trials that have assessed the effectiveness of TXA on stroke patients. Lastly, the review will explore the strengths and shortcomings of TXA and make suggestions on where future research could continue to look for answers.

Types of Strokes

While hemorrhagic and ischemic strokes are similar in their effects on the human body, there are differences in their cause, progression, and overall impact on patient outcome. A stroke can be defined as any unintended interruption of normal blood flow or perfusion to the brain (Gravanis, Tsirka 2008). Ischemic stroke is caused by a blocked blood vessel in the brain, usually from a clot or plaque buildup. This blockage deprives brain tissue of fresh, oxygenated blood (Figure 2A). If left untreated, this ischemia will rapidly progress to infarction, or tissue death (Sekerdag et al. 2018). Hemorrhagic stroke is similar to ischemic stroke in that the brain is starved of oxygenated blood. In hemorrhagic stroke, however, this starvation is caused by a leak in the circulatory system. Typically, the result of a ruptured aneurysm or weakened arterial wall, leaks result in blood spilling out into the surrounding intracranial space (Figure 2B). As with any external bleeding, this leak in the system prevents oxygen exchange in the tissue. Named for the hemorrhage that occurs in the brain from a ruptured blood vessel, this type of stroke will also lead to infarction, as well as additional problems.

“Time is brain” is a saying used in emergency medicine to succinctly convey the seriousness of cerebral infarction. Irreparable brain damage begins immediately upon loss of perfusion, with millions of neurons, billions of synapses, and miles of nerve fiber destroyed every minute. For every hour that passes while oxygen is prevented from reaching its destination in the brain, 3.6 years are shaved off the patient’s life in terms of brain function (Saver 2006). Assuming they survive, stroke patients will often fight lifelong physical and mental disability, in addition to things like depression, social reclusiveness, loss of independence, and increased risk for developing additional future strokes. Due to the common occurrence and terrible outcomes of stroke, early recognition of its onset by family, friends, and bystanders is crucial to survival.

Stroke can be recognized by several hallmark signs and symptoms. Those associated with ischemic stroke are very similar in outward appearance to those associated with hemorrhagic stroke. These signs include hemiparesis, or motor weakness and lack of sensation in either the left or right side of the body. Hemiplegia, or total paralysis of one side of the body, is also common. These conditions may manifest themselves as an uneven smile, a lazy eye, a limp, or an arm that won’t move while the other works fine. Prolonged lack of oxygen in the brain can result in convulsions, posturing, loss of control over bodily functions, and eventually full loss of consciousness and responsiveness. Symptoms range from headaches to phantom sounds, smells, and sensations. Patients may report dizziness, nausea, and lightheadedness.

Due to the time sensitive nature of stroke and the current lack of simple treatment, early recognition and diagnosis are crucial components of modern stroke care. Together, recognition of these signs constitutes the Cincinnati Prehospital Stroke Scale. Often referred to simply as FAST or ‘Face, Arm, Speech, Time (Zohrevandi, et al. 2015), this scale focuses on the highly noticeable detriments to facial expressions, arm coordination, and coherent speech. The FAST scale applies to both ischemic and hemorrhagic strokes, as their externally visible signs are very similar, especially in
the early stages and when viewed by non-medical laypersons. Even medical professionals have difficulty differentiating between the ischemic and hemorrhagic varieties without the aid of advanced imaging techniques, like CT or MRI scans (Figure 2). This can become problematic when treatment specific to one type of stroke is needed.

Such scanning equipment is unavailable to first responders and may even be absent at smaller hospitals, particularly rural ones. This poses a serious challenge to the use of some medications for both hemorrhagic and ischemic stroke patients. Their treatment often revolves around either the destruction or formation of clots to either enable or restrict blood flow, depending on what is causing the stroke. Because of this, TXA may not be approved for stroke use on ambulances, urgent care clinics, and at small emergency departments that lack imaging capabilities. This could seriously limit the potential effectiveness of the drug, considering providers in these settings are often the first to encounter the patient. Multiple trials studying TXA for stroke use concede that early administration of the drug is key to its efficacy (CRASH-3 trial collaborators 2018, Sprigg et al. 2019).

In the absence of robust medical cures, preventative care and management of risk factors have become important ways to combat the impact of stroke. Some of the most common reasons for stroke are sustained elevated blood pressure, diabetes, smoking, obesity, high cholesterol, and heart conditions such as congestive heart failure. Stress levels, alcohol and illicit drug usage, oral contraceptives, and genetic predisposition are additional contributors. Stroke can also be a side effect of other dangerous conditions. Traumatic brain injury (TBI) is one of the leading causes of hemorrhagic stroke (CRASH-3 trial collaborators 2019). Bleeding in the brain caused by TBI sustained in common occurrences like car accidents or contact sports can quickly progress to a life-threatening situation.

In an attempt to manage risk factors, prescription of anticoagulants may also indirectly contribute to the danger of hemorrhagic stroke. They’re often prescribed to people who are at risk of having a heart attack or stroke (Polymeris et al. 2023). Ironically, anticoagulants, while decreasing risk of ischemic stroke, can actually increase the risk of having a hemorrhagic one. These drugs, often referred to as blood thinners, are commonly used by geriatric patients—a demographic that is particularly susceptible to experiencing falls. Falls are a leading cause of head trauma in these patients, and head trauma is a leading cause of hemorrhagic stroke.

Hemorrhagic stroke, often called intracerebral hemorrhage (ICH), is particularly dangerous and imparts a much higher mortality rate on patients than ischemic stroke. ICH accounts for only about 20% of all strokes, yet disproportionately represents stroke related death, being responsible for 40-50% of the mortality of strokes (Sprigg et al. 2018). The increased lethality of this stroke variety is because blood is spilling out through the ruptured artery. Beyond simply preventing oxygen from reaching parts of the brain, ICH has additional devastating consequences. Because the brain is encapsulated within the skull, there is very limited space for it to expand due to swelling, inflammation, and bleeding. Much like a bruise on your arm swells outwards as blood pools beneath the surface of the skin, a hematoma in the brain also swells with blood. The difference here is that instead of pushing outwards against soft skin, the brain cannot push past the skull. The pressure exerted by the blood pushes back against the brain, resulting in additional cell damage.
As more and more smaller blood vessels are constricted, secondary ischemic effects occur (Figure 2B). Hematoma expansion (HE) refers to additional movement of the bruised portion deeper into the brain (Liu et al. 2021). This is visible by comparing two or more CT scans taken over a period of time. Monitoring the shift of this expansion is critical to determining how aggressively to treat the stroke. Hematoma expansion is often used as a marker of poor prognosis due to the seriousness of the impending side effects. Around 25% of patients with hemorrhagic stroke will develop HE (Sprigg et al. 2018).

Intracranial pressure is a severe complication of hemorrhagic stroke. At the same time, parts of the brain unaffected by the pressure are still being deprived of oxygen because the blood is flowing out of the vessel at the bleed site before it can reach its destination. (Liu et al. 2021, Polymeris et al. 2023). The other part of the higher mortality rate for hemorrhagic stroke comes from secondary complications. These are conditions that occur as the result of a side effect from some treatment for the initial stroke. For example, medically induced comas for stroke recovery can also lead to deep vein thrombosis. This occurs when blood clots form in the legs due to a lack of circulation. These clots can cause a range of problems on their own but can be especially dangerous if the clot breaks off from its original site and travels to the lungs, heart, or brain. Thus, deep vein thrombosis can be a cause of additional strokes. Lastly, brain herniation represents the most severe and bleak outcome for ICH patients. This is when pressure inside the skull is so great that it pushes the brain down into the large hole at the base of the skull where the spinal cord connects.

Though hemorrhagic and ischemic strokes differ in their cause, both produce the same devastating result: death of brain tissue. Their similar outward presentation leads to a tricky situation for medical providers, who must quickly discern which one they are dealing with to formulate an effective treatment plan. The dangers of misdiagnosing one type of stroke as another are great, as treatment depends greatly on which type the patient presents with. In the past few decades, care for ischemic stroke has improved with the use of clot dissolving medicines like tPA. Despite this, there is no such widely accepted and approved treatment for hemorrhagic stroke victims (Sprigg et al. 2018). The main treatments for ICH are blood pressure monitoring, advanced imaging, and surgery if indicated.

If the patient does not respond well to medication, monitoring, and rest, then surgery is needed. A technique at the forefront of hemorrhagic stroke care is coil embolization, where a catheter is inserted and guided to the hemorrhage site to block blood flow. This option, though effective, is costly, invasive, and carries risk of complication (Medical Advisory Secretariat 2006). Considering the monetary expense and risk involved in such procedures, researchers have been searching for a cost-effective non-invasive alternative to surgery. Similar to how tPA has revolutionized ischemic stroke care, many have looked to tranexamic acid as a potential cure for hemorrhagic stroke patients.

Tranexamic Acid

Tranexamic acid is what’s known as an antifibrinolytic medication. Fibrin is a protein found in human blood that is responsible for clot formation. Plasmin is the enzyme that causes degradation of fibrin and thus a reduction in the capability of the blood to form clots. Antifibrinolytics are drugs
that prevent the degradation of fibrin in the blood, thus indirectly boosting clotting. Antifibrinolytics are different from clot promoters in that they prevent degradation of clots already formed, as opposed to actively increasing the number of clots or increasing the likelihood of a clot forming (Chapin, Hajjar 2015).

TXA is a synthetic chemical that mimics the structure and function of the amino acid lysine. It blocks the lysine receptors needed to activate plasminogen, preventing the conversion of plasminogen to plasmin (Law, et al. 2021). This lowers the amount of plasmin in the blood and thus reduces the breakdown of blood clots. By allowing clots to form, TXA is able to reduce blood loss from open wounds. It is this mechanism that researchers hope to exploit to achieve a similar effect at stopping the internal bleeding found in some types of strokes. However, because of its effects on the conversion of plasminogen to plasmin, TXA may have competing effects with the ischemic stroke medication tPA. Naturally present in the body as a plasminogen activator, tPA is given in concentrated doses to dissolve ischemic blood clots. Lysine analogues like TXA can prevent the breakdown of clots even in the presence of clot-busting medicines like tPA (Krishnamurti, et al. 1994). This could have serious consequences in cases of stroke misdiagnosis, e.g., if an ischemic stroke patient is mistakenly given TXA, subsequent doses of tPA would have reduced effectiveness.

TXA has a decades long history of use in the medical field for prevention of bleeding from different sources. Listed on the World Health Organization’s list of essential medications, it’s used to stop bleeding when conventional approaches like direct pressure, bandaging, tourniquets, stitches, and whole blood transfusion cannot be used or are simply insufficient. Examples of such situations are excessive nosebleeds, post-partum hemorrhage, and menorrhagia (WOMAN trial collaborators 2017). TXA is also commonly used in conjunction with conventional blood loss control methods in multi-systems trauma patients. Patients at risk of exsanguinating levels of hemorrhage, e.g., those with grievous wounds from gunshots, stabbings, high speed motor vehicle accidents, and falls from significant heights, do well when treated with TXA alongside transfusion and surgical intervention (Roberts et al). Two major studies in the early 2010’s were pivotal in cementing TXA’s role in trauma care after reporting significant reductions in mortality for patients who received the drug.

The MATTERS (Military Application of Tranexamic Acid in Trauma Emergency Resuscitation Study) of 2012 compared the outcome of trauma patients who received TXA and blood transfusion to those who received only transfusion with no TXA. The TXA cohort saw reduced mortality when compared to the non-TXA cohort. TXA was also more beneficial in severely injured patients who needed 10 or more units of blood transfused (Figure 3). The MATTERS recommended TXA be integrated into trauma protocols, particularly in cases of extreme blood loss (Morrison et al. 2012).

One year later, the CRASH-2 (precursor to the aforementioned CRASH-3) produced similar evidence for TXA’s success in preventing hemorrhage. CRASH-2 looked at the effect TXA had on patient mortality and likelihood of blood vessel occlusion. Over 20,000 eligible patients were randomly assigned either TXA or a placebo and then evaluated for changes in condition. Significantly reduced all-cause mortality was seen in the TXA group when compared to the placebo (p=0.0035). There was no major difference in incidence of occlusive events between the two groups (Roberts et al. 2013).
In addition to proven effectiveness, another positive factor for TXA use is that side effects are typically mild (Colomina et al.). Most adverse, unintended effects are limited to acute abdominal discomfort, e.g., nausea, vomiting, diarrhea, and cramping. Rarely, more serious complications can arise, for example seizures. In the worst-case scenarios, TXA has been linked to detrimental clotting. This is especially concerning for patients with a history of, or increased risk of, developing ischemic stroke (Liu, et al. 2021). This contrasts with CRASH-3 findings, which reported that detrimental clotting effects were just as likely to occur in TXA groups as placebo groups. No negative side effects or safety concerns are known when using TXA to treat post-partum bleeding (WOMAN trial collaborators 2017.)

The key indication for the use of TXA is hemorrhage that is unable to be controlled by the body’s natural clot formation (Morrison, et al. 2012). It’s most often used in cases of severe trauma but also for cases of excessive nosebleeds and menorrhagia. TXA was shown to reduce mortality in patients with post-partum hemorrhage (WOMAN trial collaborators 2017). It may be used during surgery to reduce blood loss from incisions as well. Though TXA is not currently FDA approved to treat intracerebral hemorrhage, some evidence shows that it may be effective at reducing stroke death (CRASH-3 collaborators 2019). This, however, is the subject of ongoing debate.

Like most medications, there exist some instances in which administration would be inappropriate. Such situations are known as contraindications, and they preclude the use of a particular drug or procedure. Contraindications for TXA are patient history of ischemia, including prior ischemic stroke, heart attack, deep vein thrombosis, or pulmonary embolism (Liu, et al. 2021). These conditions could worsen or recur under the use of TXA, due to its nature regarding clots. In addition to known history of ischemic stroke, it is imperative that medical providers are able to confidently rule out ischemia from being the primary cause of the patient’s current condition. Should TXA be given to a patient experiencing an ischemic stroke, there is little chance any benefit may occur, and it could exacerbate the stroke symptoms (Liu et al. 2021).

**TXA as a Treatment for Stroke**

Given its current uses, its indications, contraindications, and side effects, is TXA a viable option for hemorrhagic stroke patients? Could it exist as a middle ground between passive monitoring and risky, expensive surgical procedures? Those are the questions that the researchers behind recent trials are aiming to answer. Bolstered by the past success of TXA for treating traumatic bleeding and motivated by a lack of medicines for treating ICH, some have been keen to sing its praises. However, there are many in the medical community who remain skeptical. Even if proven effective, there are still pros and cons to weigh.

Following the decades of use for other conditions, several recent studies have attempted to prove TXA can also be used to stop internal bleeding within the brain. The CRASH-3 trial was a large, randomized controlled trial conducted at multiple hospitals around the world. It enrolled 12,737 ICH patients and randomly assigned them either TXA or placebo. The patients were evaluated using the Glasgow Coma Scale (GCS), which assesses neurological function. Patients that exhibited moderate brain damage were found to have reduced risk of death when given TXA vs those with moderate to severe injuries (p=0.007) (Figure 4). There was a correlation between the elapsed time until TXA administration and patient outcome. The faster the drug was administered,
the more likely it was to prevent patient death (CRASH-3 collaborators). This is consistent with the results of non-stroke related studies, e.g., the WOMAN trial found that early administration significantly improved outcome when given for post-partum blood loss.

Citing the CRASH-3, several subsequent studies have contributed to the ongoing discussion regarding TXA use for hemorrhagic stroke. TRAIGE (Tranexamic acid for acute intracerebral haemorrhage growth based on imaging assessment) was a randomized and placebo-controlled study that evaluated TXA use specifically in patients with hematoma expansion (HE). In the study, 696 patients were evaluated and randomly assigned either TXA or placebo. TRAIGE found that TXA did not reduce brain hemorrhage in any subgroup. It did not significantly reduce HE in stroke patients either (p=0.89) (Figure 5). The authors of this paper noted that by virtue of their focus on patients with hematoma expansion, TXA may show reduced efficacy given the severity of the condition. Recall that measurable HE is an indicator of poor patient outcome (Liu et al. 2021).

The TICH-2 (Tranexamic Acid to Improve functional status in adults with spontaneous intracerebral hemorrhage) was another randomized, placebo-controlled trial, in which 1,161 hemorrhagic stroke patients were enrolled and randomly given TXA or a placebo. Relative to placebo, TXA had no impact on long-term outlook in ICH patients (p=0.11); however, TXA did reduce hematoma expansion and did not contribute to detrimental clotting (Sprigg et al. 2018). Following the TICH-2 trial, the TICH-NOAC, a randomized controlled trial in Switzerland, aimed to explore the effect of TXA on stroke patients who were also taking a non-vitamin K oral anticoagulant (NOAC). These anticoagulants are commonly prescribed to people with risk factors for ischemic stroke. The TICH-NOAC trial found only a 7% reduction in HE for patients given TXA over the placebo, which was statistically insignificant (Figure 6). Likewise, TXA did not reduce all-cause mortality by the 90-day mark (Polymeris, et al. 2023).

A meta-analysis of 25 different papers, including the CRASH-2 and 3, TRAIGE, and TICH-2 papers mentioned in this review, found that TXA use resulted in overall significant reduction in hematoma expansion (p=0.001) (Xiong et al. 2023). However, TXA did not reduce mortality, nor did it show any positive effect on patient disability. This meta-analysis includes results from studies that looked at hemorrhagic strokes caused by a traumatic brain injury in addition to those caused by spontaneous vessel rupture. It remains unclear whether TXA would behave differently depending on what initially caused the stroke.

In addition to the mounting evidence that appears to contradict the CRASH-3 authors’ claims that TXA reduces ICH related death, there are questions being raised regarding the nature of that claim itself. The authors did not mention in their conclusion that TXA was only shown to reduce death in a single subset of their patients (those with the mildest symptoms). Mansukhani et al. found discrepancies in time to treatment numbers reported by the authors in their 2020 review of the paper. Proponents of the CRASH-3 study point to its large sample size and randomized and placebo-controlled methods. Though many of the subsequent trials studying the use of TXA for hemorrhagic stroke patients have much smaller patient cohorts, they all utilized similarly robust methods.

TXA has been shown time and again to be a successful antifibrinolytic agent when used to control hemorrhage associated with trauma. It’s cheap, easy to use, and has mostly mild side effects
(Roberts et al. 2013). However, conflicting reports on its efficacy regarding intracerebral hemorrhage seem to be at odds with expected results (Shi et al. 2022). Despite its effectiveness at stopping blood loss in myriad situations, more research is needed to definitively say whether the drug can treat bleeding within the brain. Of the trials that showed positive results for TXA use, most were limited to patients with mild to moderate severity. All trials showed increased effectiveness the earlier TXA was administered, highlighting the importance of symptom recognition and CT/MRI scanning. In conclusion, TXA appears to be relatively safe and effective when given early to patients with confirmed hemorrhagic stroke, with diminishing returns according to level of brain damage. Further research on TXA should be conducted, as well as investigation into other antifibrinolytic drugs and different derivatives of Lysine. Additionally, other parts of the clotting process should be explored to see if brain hemorrhage can be treated without the use of antifibrinolytics.
References


Figure 1.

Concept diagram depicting the relationship between the types of strokes.
Figure 2

Comparison of CT scans for the two types of strokes. Contrast dye causes blood to appear white. Similarly, perfused tissue appears lighter in color than ischemic tissue.
TXA significantly improved survival of trauma patients at every follow-up interval ($p=0.006$) (Morrison et al. 2012).

Figure 3
Patients with mild to moderate brain damage (GCS > 8) benefited from tranexamic acid. TXA did not improve outcome in patients with GCS < 9. TXA did not increase the risk of unintended occlusive events (CRASH-3 trial collaborators 2019).
TXA did not significantly reduce hemorrhage in any subgroup (Liu et al. 2021)
Figure 6

TXA did not prevent or reduce hematoma expansion relative to the placebo (Polymeris et al. 2023)