Thesis

The Use of Tranexamic Acid in Traumatic Brain Injury

Submitted by

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Declaration of Academic Integrity

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Graz, am 19.08.2024 Irma Rathofer eh.

Danksagungen

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Zusammenfassung

Einleitung: Seit der erstmaligen Synthese von Tranexamsäure (TXA) in den 1960er-Jahren hat das Medikament zunehmend Bedeutung bei der Behandlung diverser Krankheitsbilder gewonnen, vor allem jener die mit starkem Blutverlust einhergehen. Dies ist in der Notfallmedizin, vor allem bei Traumata, der Fall. Während hier Blutverlust die häufigste Todesursache darstellt, sind Schädel-Hirn-Traumata (SHT) durch die Schädigung von Gehirn und umgebenden Strukturen der häufigste Grund für spätere Mortalität und Morbidität. In aktuellen Studien wurde nun untersucht, ob die Anwendung von Antifibrinolytika wie TXA, über die Hemmung der Fibrinolyse durch eine verminderte Aktivierung von Plasmin, eine Verbesserung des Überlebens und der neurologischen Funktion nach einem SHT mit sich bringt.

Methoden: Auf Basis einer umfangreichen Literaturrecherche mittels PubMed wurde eine Übersichtsarbeit verfasst. Dazu wurden 5 doppelt- oder einfach-verblindete, randomisierte und Placebo-kontrollierte Studien berücksichtig, in denen Patientinnen und Patienten mit einem SHT entweder TXA oder ein entsprechendes Placebo zusätzlich zur Standardtherapie erhielten. Die Endpunkte, die untersucht wurden, waren einerseits die Mortalität und andererseits die neurologische Funktionalität zu verschiedenen Zeitpunkten nach dem Trauma. Zusätzlich wurde versucht zu ermitteln, ob das Medikament auch einen Einfluss auf das Fortschreiten von traumatischen, intrakraniellen Blutungen hat. Die Studienergebnisse wurden weiters verglichen und diskutiert.

Ergebnisse: In 4 der inkludierten Studien wurde die Überlebensrate analysiert. Es konnte nicht nachgewiesen werden, dass die Gabe von TXA die Überlebensrate signifikant verbessert, mit Ausnahme von Patientinnen und Patienten mit einem milden-mittelschweren SHT, vor allem wenn TXA früh gegeben wird oder wenn die Diagnose einer intrakraniellen Blutung gestellt ist. Des weiteren konnte keine signifikant bessere neurologische Funktion in der Interventionsgruppe im Vergleich zur Placebogruppe festgestellt werden. In einer Studie konnte gezeigt werden, dass die Volumenzunahme einer traumatischen intrakraniellen Blutung durch die Applikation von TXA signifikant geringer war als bei der Kontrollgruppe.

Schlussfolgerung: Es gibt Hinweise darauf, dass die Gabe von TXA bei bestimmten Patientinnengruppen und Patientengruppen zu einer höheren Überlebensrate führen kann und auch die Ausbreitung von traumatischen intrakraniellen Hämatomen verringern oder

unterbinden kann. Es sind derzeit allerdings nicht genügend Daten vorhanden, um eine eindeutige Empfehlung für oder gegen den Einsatz von TXA beim SHT abzugeben.

Schlüsselwörter: Tranexamsäure; Schädel-Hirn-Trauma; Antifibrinolytika; Koagulopathie; Mortalität; Neurologische Funktion; Intrakranielle Blutung

Abstract

Introduction: Since Tranexamic Acid (TXA) was first synthesised in the 1960s, it has become increasingly relevant in the treatment of medical conditions that are associated with substantial blood loss. In critical care medicine this is particularly relevant in the context of trauma. Blood loss is the most common cause of early death in trauma patients, while traumatic brain injury (TBI) is the most frequent origin of delayed death and morbidity due to injuries to brain and its encasing structures. Current studies have set out to determine, whether the application of antifibrinolytic drugs such as TXA, which inhibits fibrinolysis via reducing the activation of plasmin, can have beneficial influences on mortality rates and neurologic function of patients after TBI.

Methods: The basis of this thesis was extensive literary research conducted on PubMed. Five single- or double-blinded, randomised and placebo-controlled trials were included. Each of them compared the application of TXA to a placebo in patients who suffered TBI, in addition to other standard therapies. The examined endpoints were mortality, functional neurologic outcome at different times after injury and progression of intracranial haemorrhage. The trial results were then compared and discussed wherever feasible.

Results: Mortality was an outcome included in 4 of the trials. It was not possible to prove a statistically significant decrease of the mortality rate. The exception were patients with mild-moderate TBI, in particular when the medication was applied soon after injury, and patients who were diagnosed with intracranial haemorrhage. There were no significantly improved neurologic outcomes in the intervention groups compared to the control groups. One trial found that there was a significantly reduced progression of traumatic intracranial haemorrhage in patients treated with TXA in contrast to those who received the placebo.

Conclusion: The results suggest that application of TXA may reduce the mortality rates of specific patient groups after TBI and reduce or impede the progression of traumatic intracranial haemorrhage. However, the currently available data is not conclusive enough to give a general recommendation regarding the application of TXA in TBI.

Keywords: Tranexamic Acid; Traumatic Brain Injury; Antifibrinolytic; Mortality; Neurological Outcome; Intracranial Haemorrhage

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Abbreviations and their Meanings

ADP	Adenosine Diphosphate
AT	Antithrombin
BBB	Blood-Brain Barrier
CAS	Contact Activation System
CBF	Cerebral Blood Flow
CO	Cerebral Oedema
CPP	Cerebral Perfusion Pressure
CSF	Cerebro-Spinal Fluid
CT	Computed Tomography
DBP	Diastolic Blood Pressure
DIC	Disseminated Intravascular Coagulation
DRS	Disability Rating Scale
DVT	Deep Vein Thrombosis
GCS	Glasgow Coma Scale
GOS	Glasgow Outcome Scale
GOSe	Glasgow Outcome Scale – extended
HMWK	High-Molecular-Weight Kininogen
ICH	Intracranial Haemorrhage
ICP	Intracranial Pressure
IL	Interleukin
IM	Intramuscular
ISS	Injury Severity Score
IV	Intravenous

MAP	Mean Arterial Pressure
MI	Myocardial Infarction
mmHg	Millimetre Mercury
PAI	Plasminogen Activator Inhibitor
PE	Pulmonary Embolism
PEA	Phosphatidylethanolamin
PIH	Progressive Intracranial Haemorrhage
PS	Phosphatidylserin
PT	Pulmonary Thrombosis
RCT	Randomised Controlled Trial
RR	Risk Ratio
RSI	Rapid Sequence Induction
SBP	Systolic Blood Pressure
SIADH	Syndrome of Inadequate Antidiuretic Hormone Secretion
TBI	Traumatic Brain Injury
TF	Tissue Factor
TIC	Trauma-Induced Coagulopathy
TNF	Tumour Necrosis Factor
tPA	Tissue Plasminogen Activator
TXA	Tranexamic Acid
TxA2	Thromboxane A2
uPA	Urokinase
VTE	Venous Thromboembolism
vWF	von-Willebrand Factor

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1 Introduction

Globally, traumatic brain injuries (TBI) are the leading cause of mortality and morbidity in adults under the age of 45 years. According to studies, TBI often occurs due to sport injuries and motor vehicle crashes and can lead to long-term neurological deficits, behavioural alterations and cognitive decline, which can have a considerable impact on a person's life and strain public health resources. Furthermore, TBI can disrupt the blood-brain-barrier (BBB) leading to the distribution of brain-derived molecules into the systemic circulation as well as inducing a hypercoagulable and hyperfibrinolytic state. (1,2)

Tranexamic acid (TXA) is an antifibrinloytic drug first synthesised in 1962 and its use has since been recommended in various bleeding conditions. The Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage-2 (CRASH-2) study conducted in 274 hospitals in 40 countries found that the administration of TXA significantly reduced all-cause mortality at 28 days. Continuous bleeding in patients suffering from traumatic brain injuries can lead to an increased intracranial pressure (ICP), which is associated with higher mortality as well as unfavourable outcomes. It has been suggested that the administration of TXA can reduce the progression of intracranial haemorrhage (ICH) and therefore lessen brain herniation, leading to better clinical outcomes. (3,4)

While it can be said that TXA is usually well-tolerated by patients and the associated adverse effects are mostly mild, there is also the possibility of more serious side effects such as severe thromboembolic complications including pulmonary embolism (PE) , deep venous thrombosis and cerebral thrombosis. Furthermore, the evidence to clearly support the recommendation for the use of TXA in TBI is currently still limited.(4)

The aim of this thesis is to summarise studies administering TXA in TBI and evaluate its influence on mortality.

1.1 Traumatic Brain Injury

1.1.1 Definition

TBI can be defined as impairment of neurological function following external application of force to the head. The clinical presentation can vary greatly with symptoms ranging from slight confusion to coma and even death. In males the prevalence of TBI is twice as high as in females and the distribution of age is trimodal. The peaks in prevalence are 0-4 years, 15-

24 years and >75 years of age. While motor vehicle accidents are the most common cause in children and young adults, it is more common for the elderly to suffer TBI following a fall. Furthermore, in modern warfare TBI is considered a “signature injury”. (5)

The majority of patients with traumatic brain injuries also experience trauma to the facial skull, the extremities, the spine, the thorax, abdomen or pelvis. When classifying TBI, it is crucial to evaluate the severity and to differentiate whether it is open or closed, and whether other injuries are also present.(6)

The determining factor of differentiating closed versus open TBI is whether there is an injury of the dura mater. In closed TBI the dura is intact, whereas it is injured in an open TBI, the most extreme case being a penetrating head injury. (6)

Initially there may be changes to vigilance, either qualitatively or quantitatively due to diffuse axonal injury and/or focal contusion of brain tissue. The duration of these changes can also be used to categorise the severity of TBI. If they last for less than 15 minutes, it qualifies as mild TBI, a duration between 15 minutes and 24 hours as moderate and a duration of more than 24 hours is categorised as severe.(7)

1.1.2 Classification using the Glasgow Coma Scale

The severity of TBI can be classified as mild, moderate or severe using the Glasgow Coma Scale (GCS). There are three components considered in the GCS (see Table 1): Eye opening response (1-4 points), best verbal response (1-5 points) and the best motor response (1-6 points). Mild TBI (frequently also referred to as “concussion”) accounts for more than 80% and is defined as a GCS of 14 to 15. Approximately 10% of all head injuries can be categorised as moderate TBI with a GCS of 9-13. While the mortality rate for patients with moderate TBI is less than 20%, the percentage of those suffering from long-term disability can be higher. Roughly 40% of the individuals with moderate TBI present with abnormal findings in the CT scan and nearly 10% need to undergo neurosurgical intervention. A GCS of 3-8 is classified as severe TBI with a mortality rate up to 40% and a rate of good recovery of <10%. (5)

However, it is important to consider that there might be a diagnostic gap when only using GCS to assess TBI severity, in particular when only the sum is taken into consideration. For instance, an elevated ICP can initially present as spontaneous (rather than motor response to pain) abnormal extension of the extremities, which are not considered in the GCS.(8)

Points	Eye opening response	Best verbal response	Best motor response
6			Follows commands
5		Alert and oriented	Moves to localised pain
4	Spontaneously	Disoriented conversation	Moves/withdraws to pain
3	To speech	Nonsensical speaking	Abnormal flexion to pain (decorticate)
2	To pain	Moans, unintelligible sounds	Abnormal extension to pain(decerebrate)
1	No response	No response	No response

Table 1 Glasgow Coma Scale (GCS). Points are awarded in three categories: eye opening, best verbal and motor response. The highest possible score is 15, the lowest 3. Mild TBI: 15-13 points. Moderate TBI: 12-9 points; Severe TBI: 8-3 points. Adapted from Tintinalli J. (5)

1.1.3 Pathophysiology

1.1.3.1 Autoregulation and Cerebral Blood Flow

In order to maintain adequate neurological function, it is crucial that the delivery of oxygen and nutrients to the brain as well as the removal of cellular waste match with its metabolic demands. The equilibrium is maintained by adapting the cerebral blood flow (CBF) to the current demands, a process that is called autoregulation. In adults the CBF typically amounts to approximately 50ml/100g/min. Beginning at 22ml/100g/min loss of cerebral function can be observed and a reduction to 20-30% of the baseline CBF over several minutes causes ischaemia. Under normal circumstances autoregulation functions within mean arterial pressures (MAP) from 60millimetre mercury (mmHg) to 160mmHg to ensure cerebral perfusion pressures (CPP) >50mmHg and ICP within the range of 5-15mmHg. Outside of these limits of autoregulation the CBF can no longer be controlled to provide sufficient blood flow for normal brain function. The formulas used to calculate factors affecting CBF are the following:(9-11)

CPP = MAP-ICP
MAP = DBP+(SBP-DBP/3)
CBF = CPP/CVR [1]
CVR = CPP/CBF

Table 2 Formulas used to calculate relevant parameters of cerebral perfusion. CPP: cerebral perfusion pressure; MAP: mean arterial pressure; DBP: diastolic blood pressure; SBP: systolic blood pressure; CBF: cerebral blood flow; CVR: cerebral venous resistance

The formulas and their influence on CBF will be explained on the following pages. There are at least four mechanisms proposed to influence autoregulation: myogenic, neurogenic, metabolic and endothelial mechanisms. The myogenic component describes the ability of smooth muscle in the wall of blood vessels to dilate or constrict in response to transmural pressure changes. The neurogenic element relates to the vast vascular innervation, facilitating vasoconstriction, while the metabolic component characterises the changes in the vascular resistance due to shifts in the concentration of protons and the arterial partial pressure of carbon dioxide ($PaCO_2$). The $PaCO_2$ correlates closely with the CPP and therefore also with the CBF. Hypercapnia leads to cerebral vasodilation and increased perfusion, hypocapnia causes the opposite. With every change of 1 mmHg $PaCO_2$ the cerebral perfusion increases or decreases about 2ml/min/100g brain tissue within several minutes. Lastly, the endothelial mechanism includes the effects of endothelial factors, such as nitric oxide (NO), on autoregulation of the brain.(9,10,12)

An impairment of autoregulation may develop after trauma and can be transient or permanent. When the CPP drops below 50 mmHg, autoregulation fails resulting in ischaemia of brain tissue. Looking at the formulas mentioned above, CPP is influenced mainly by the MAP and ICP. If the latter rises above 15mmHg (for example due to bleeding or swelling following TBI), MAP also has to increase to ensure adequate cerebral perfusion. This physiological response of the nervous system to acute intracranial hypertension is called the Cushing reflex. Initially, the sympathetic nervous system causes an increase in the blood pressure and heart rate to overcome the elevated ICP, later the patients become bradycardic and begins to exhibit a pattern of irregular respiration. These three pathologies are referred to as the Cushing triad and while the underlying mechanisms are not entirely clear yet, the common notion is that bradycardia is a sign of exacerbating intracranial pathologies while the irregular breathing results from brainstem dysfunction due to compression or

[1] Simplified according to Hagen-Poiseuille‘s law

haemodynamic abnormalities. Another compensatory process to counteract the diminished delivery of oxygen to the brain is a higher extraction of oxygen, which is however only possible to a limited extent. (1,13,14)

According to the Monro-Kellie doctrine, the total volume of brain tissue, blood and cerebro-spinal fluid (CSF) is constant inside the rigid skull. If there is an increase in one of these components, the other components will try to compensate, resulting in a decrease of their volume. Assuming the volume of brain parenchyma stays constant, blood flow has a larger impact on volume dynamics than CSF. If the intracranial volume rises, in an acute setting usually blood or oedema, and compensatory measures have been exhausted, an increase in ICP occurs. (15,16)

1.1.3.2 Primary Injury

Primary injury in TBI is caused by mechanical forces during the initial insult, causing direct damage to brain parenchyma. This includes brain contusions, traumatic intracranial bleeding and diffuse axonal damage. (5)

Most commonly contusions occur in the frontal and temporal as well as the occipital lobe and are frequently associated with subarachnoid haemorrhage. This type of injury can be found at the location of blunt trauma or on the opposite side of trauma (known as contrecoup injury). It may present in unconsciousness as well as headaches and memory loss (antero- and retrograde). Other neurological functions may be impaired as well, occasionally leading to life-long neurological deficits. (5,6)

Diffuse axonal damage is caused by shear forces, damaging axons and surrounding blood vessels. The tearing of axons in certain regions is often not noticed immediately but can lead to the degeneration of associated neural pathways over the course of several weeks and months. (6)

Traumatic intracranial bleedings occur when blood vessels are injured during trauma. There are four types of bleedings that can also be found simultaneously: epidural, subdural, subarachnoid and intracerebral haemorrhage.(7)

Epidural bleeding is defined as a bleeding between the calvaria and dura mater. The source is usually the middle meningeal artery or one of its vascular branches and is therefore most commonly found around the temporal lobe. In many cases, vascular injury is caused by a skull fracture in close proximity of the vessel, but it may also occur without any damage to

the calvaria. Epidural bleeding typically presents as unconsciousness directly following trauma, afterwards there might be a period with little to no symptoms that can last for several hours, followed by coma. Other characteristic symptoms include headaches, nausea, vomiting and agitation as well as skull fractures. Furthermore, there might be homolateral mydriasis due to the compression of the oculomotor nerve as well as contralateral hemiparesis.

Subdural bleeding is the formation of a haematoma between the dura and the arachnoid mater, typically following the rupture of bridging veins. The symptoms can develop acutely after trauma or over the course of several days and weeks. Subdural and epidural bleeding have very similar clinical presentations, and it is therefore not possible to distinguish the two without further imaging. Chronic subdural bleedings on the other hand are often less apparent presenting with confusion, amnesia and psychomotor retardation several weeks or months after minor head trauma.

Bleeding into the subarachnoid space, which is located between the arachnoid and pia mater is referred to as subarachnoid haemorrhage. It is frequently associated with contusions of the cortex and intracerebral bleedings. The main symptoms are meningism and severe headaches accompanied by progressive loss of vigilance, nausea and vomiting.

Bleeding into the brain parenchyma is referred to as intracerebral haemorrhage and is usually the result of injury to small intracerebral vessels following contusions. These types of bleedings are frequently located around the frontal and temporal lobe close to the cortex. Symptoms vary depending on location and expansion of the haematoma. They may include a focal deficit or, in case of larger bleedings, reduced vigilance. (6,7)

1.1.3.3 Secondary Injury

Primary injuries commonly progress into what is described as the secondary neurotoxic cascade, a delayed and prolonged series of cellular and subcellular events, causing further damage to the brain ultimately leading to poorer neurological outcomes. It includes several factors: excitotoxicity, mitochondrial dysfunction, oxidative stress, lipid peroxidation, neuroinflammation, axon degeneration and apoptotic cell death. These secondary injury mechanisms however should not be confused with secondary insults. The term secondary insults is used to describe circumstances and conditions such as hypotension and hypoxaemia that lead to an acceleration of neuron damage and therefore worsen the long

term outcome. The prevention of these conditions is an important component in the treatment of TBI and will be discussed in the following chapters. (5,17)

Excitotoxicity

Studies have demonstrated that neuronal cell death and the disruption of the BBB caused by TBI leads to an increased release of excitatory amino acids, such as aspartate and glutamate, from the presynaptic nerve ending. The amount of glutamate in the synaptic cleft is further increased by a disruption of glutamate re-uptake transporters. The presence of excitatory amino acids activates both ionic (such as the N-methyl-d-aspartate/NMDA) and metabotropic (such as α-amino-3-hydroxy-5-methyl-4-isoxazole propionate/AMPA) glutamate receptors, which are ligand-gated ionic channels. The activation of NMDA-receptors leads to an influx of sodium and calcium ions, which activate a downstream cascade of signals ultimately leading to the production of reactive oxygen species (ROS) and NO, which both aggravate cell injury. (17)

Mitochondrial Dysfunction

Mitochondrial dysfunction is one of the main factors in the pathophysiology of TBI. The activation of NMDA-receptors by glutamate leads to an excessive influx of ions and the sequestration of calcium ions inside the mitochondria leads to production of ROS, depolarisation of the mitochondrial membrane and inhibition of adenosine triphosphate (ATP) synthesis, causing the breakdown of the electron transport chain and impairing oxidative phosphorylation of glucose. While anaerobic glycolysis can compensate for the disrupted oxidative phosphorylation, it also increases lactate as a glycolytic product. This cascade culminates in the disruption of metabolic reactions for cell survival. Additionally, the dysregulation in the cellular calcium homeostasis is aggravated by concomitant influx of sodium ions and deprivation of ATP which both impede the function of sodium/calcium exchangers. This leads to the activation of the mitochondrial permeability transition pore (mPTP) and a higher permeability of the inner mitochondrial membrane. Analysis of mitochondria from the human brain after TBI under the electron microscope show significant swelling and structural damage and it has been revealed that proteins that are an integral part of apoptotic cell death, such as cytochrome c and apoptosis-inducing factor (AIF), are released into the cytosol.(17,18)

Release of ROS and Lipid Peroxidation

Evidence suggests that oxidative stress is one of the main components in the pathophysiology of TBI. Free radicals and ROS are continuously produced by various processes, including enzymatic processes, excitotoxic pathways, and mitochondrial dysfunction. These free radicals can then react with NO to produce peroxynitrate, which provokes oxidative stress. Additionally, ROS react with proteins, DNA and polyunsaturated fatty acids in membrane phospholipids forming lipoperoxyl radicals, which further damage cell membranes. The changes in cell membrane permeability subsequently alter ion transportation and impact excitotoxicity. (17)

Neuroinflammation

In the first 24h hours after TBI, the injured brain parenchyma is infiltrated by circulating cells of the immune system due to a dysfunctional BBB. There is evidence that these leukocytes release a number of proinflammatory cytokines such as interleukin-1β (IL-1 β), interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α) as well as complement factors. Proinflammatory cytokines induce a further recruitment of leukocytes to the injured tissue, while TNF-α is an important factor in the activation of caspases that are involved in programmed cell death. Neuroinflammation then induces the recruitment of macrophages, activates microglia cells and leads to astrogliosis, which can still be observed in TBI survivors' years after the initial injury. (17)

Axonal Degeneration

Mechanical damage to the brain leads to the immediate disorganisation of the axonal cytoskeleton network and in combination with calcium-mediated proteolysis the acute axonal damage, which can be observed within minutes of TBI, may progress into secondary axotomy even months after the primary injury. This is characterised by the degeneration of the myelin sheath surrounding the axons, impaired axonal transport and the accumulation of axonal transport proteins. As a result, retraction bulbs are formed that may provoke protracted swelling of injured axons and apoptosis of neurons and oligodendrocytes. Furthermore, studies have shown an association between axonal damage and infiltration of the injured tissue by neuroinflammatory cells which contribute to neuroinflammation and secondary damage. (17,19)

Apoptotic Cell Death

Apoptosis of neurons and oligodendrocytes is a main indicator of secondary injury after TBI and can be observed even up to a year after the initial trauma in certain areas of the brain. Through the interaction of a number of neurochemical, cellular and molecular pathways there is an activation of proteases such as caspases, which are crucial to apoptotic events. Caspase-dependent mechanisms of apoptosis can be induced by the extrinsic death receptor pathway involving TNF-α or by the intrinsic mitochondrial pathway, which is activated by mitochondrial depolarisation, leading to the release of the cytochrome complex. After TBI there is also another pathway involved that may induce apoptotic cell death, namely caspase-independent apoptosis using calpains. These proteases are stimulated by degeneration of cytoskeletal proteins and release of mitochondrial proteins which translocate into the cell nucleus where they cause DNA damage. However, studies have also shown that a number of anti-apoptotic proteins are significantly upregulated in brain tissue following TBI. (17,20)

1.1.3.4 Cerebral Oedema

There is an association between an unfavourable neurologic outcome after TBI and cerebral oedema (CO) and the resulting increase of the ICP. CO is furthermore the leading cause of in-hospital mortality of patients after severe head trauma. The three types of CO are cytotoxic, vasogenic and interstitial, with mostly the former two taking a key role in TBI. Additional contributing factors to CO in TBI include a change in osmotic gradients and inflammatory responses. (14)

Interstitial CO is caused by the accumulation of fluids in brain tissue due to a higher osmolarity which may be caused by a rapid decrease of blood glucose (mostly in diabetic patients), urea (after dialysis) or sodium levels.

Cytotoxic CO occurs when cells start to swell, often caused by energy deficiency after an episode of hypoxia or ischaemia. The shortage of energy in the form of adenosine triphosphate (ATP) leads to dysfunction of the sodium-potassium-ATPase, which in turn results in an accumulation of sodium-ions and a deficiency of potassium-ions within the cell. The following depolarisation of the cell membrane and influx of chloride-ions changes the osmolarity and therefore draws water into the cells thus resulting in swelling. (21)

The third type of oedema is the result of higher permeability of brain capillaries, and therefore the BBB, which causes filtration of proteins into the tissue. The proteins change the osmolarity and draw water into the interstitial space thereby expanding it and causing

oedema. Some of the causes of vasogenic oedema include trauma, intracranial tumours and infections. (21)

Current treatments mostly aim at modifying the level of activation and inhibition of different pathways involved in oedema development, since untreated CO may result in intracranial hypertension and brain herniation. There are however no pharmacological therapies targeting brain oedema specifically, and while some approaches such as hyperosmolar solutions, hypothermia and decompressive craniectomy can effectively reduce ICP and mortality, the benefit on functional neurological outcome remains undetermined. (14)

1.1.3.5 Brain Herniation

Cerebral herniation is a potentially fatal dislocation of brain tissue from its usual location. Based on their location, hernias can be classified into extracranial and intracranial hernias. The latter can be further divided into subfalcine, transtentorial (ascending or descending) and tonsillar. Specific neurologic syndromes can be associated to the different localisations due to typical symptoms caused by further brain tissue damage via pressure necrosis, compression of cranial nerves, vascular damage and disruption of normal circulation of CSF. It is also essential to consider the possibility of different types of hernias occurring simultaneously. The main diagnostic tools include clinical examination, CT and MRI scans. (22)

Extracranial Herniation

Extracranial herniation occurs less frequently than the other types and is most commonly caused by postsurgical and posttraumatic skull defects allowing the herniation of brain tissue. This may be the case following an insufficient decompressive craniectomy in which the removed cranial piece was too small to allow the injured brain to swell without constriction and as a result the brain continues to herniate with an appearance similar to a “mushroom cap”. (22)

Subfalcine Herniation

Subfalcine herniation may also be referred to as midline shift or cingulate hernia and is the most frequent type of brain hernia. The usual cause is a mass effect due to a pathology located in the frontal, parietal or temporal lobe which pushes the cingulate gyrus down and underneath the falx cerebri to the other, healthy side. This occurs at the anterior part of the falx since it is less rigid and can therefore be displaced while the posterior part is less flexible and resists the pressure. The amount of midline shift can also be linked to the prognosis; a

deviation of less than 5 mm tends to have a fairly good prognosis while a shift of more than 15 mm is associated with poor outcomes. If there is a large amount of herniated tissue, it may constrict the corpus callosum and contralateral cingulate gyrus and the ventricular system as well, leading to dilation of the ventricles and further direct damage to brain tissue. Additional possible complications include the compression of cerebral vascular structures, leading to infarction of the corresponding areas. (22)

Descending Transtentorial Hernia

The descending transtentorial hernia is the second most common type of brain hernia. It can be further split into lateral (anterior and posterior) and central hernias and describes the shift of cerebral tissue downward and through the tentorial notch. Lateral descending transtentorial hernia occurs when parts of the medial temporal lobe are displaced. This categorisation also describes the progression of descending transtentorial hernia. The anterior subtype involves the downward herniation of the uncus toward the crural cistern whereas the posterior subtype is the displacement of the parahippocampal gyrus through the tentorial notch.

In central descending transtentorial hernia there is a downward shift of the diencephalon, mesencephalon and pons. The herniation results in compression of the oculomotor nerve, the posterior cerebral artery and midbrain as well as the cerebral aqueduct leading to hydrocephalus. If there is no intervention, brain tissue could descend even further and lead to tonsillar herniation.(22)

Ascending Transtentorial Hernia

When there is a mass effect beginning in the posterior cranial fossa forcing the cerebellar vermis and hemispheres upwards through the tentorial notch it is referred to as ascending transtentorial herniation. Other than a mass effect this type of herniation can also occur when an increased supratentorial hypertension is relieved abruptly. Since the tissue is displaced in the direction of least resistance, ascending transtentorial herniation will usually arise when the tentorial incisura is large. In the case of a small incisura the tissue will be pushed down and through the foramen magnum leading to tonsillar herniation.

Due to the upward herniation of the cerebellar vermis, there will be an additional anterior displacement and compression of the mesencephalon and cerebral aqueduct, which may in turn result in hydrocephaly. In some cases, there can be involvement of cerebral and cerebellar blood vessels generating ischaemia. (22)

Tonsillar Hernia

Tonsillar herniation is defined as the downward shifting of the cerebellar tonsils through the foramen magnum into the spinal canal. Most commonly it is the result of a downward mass effect caused by an infratentorial mass. However, it can also be the consequence of a progressing supratentorial mass and is usually linked to descending transtentorial hernia. Following the displacement there may be compression of the fourth ventricle leading to obstructive hydrocephalus or compression of cerebellar arteries resulting in cerebellar infarcts. Tonsillar herniation can cause sudden respiratory arrest due to severe neurological damage. (22)

1.1.4 Therapy

1.1.4.1 Prehospital Therapy Targets

Early and adequate interventions are of utmost importance in the treatment of moderate and severe TBI to improve the final outcome. It is recommended to aim for rapid stabilisation and transportation to a centre equipped to manage these types of injuries. Some of the most crucial measures in the early treatment of TBI is airway and blood pressure management. Furthermore, a neurological examination including the level of consciousness, the pupil size and reactivity to direct and indirect light, motor responses and GCS should be performed and documented multiple times to notice any changes in neurological function. (5,8)

Airway and Breathing

Following head trauma, patients with insufficient spontaneous breathing or unconscious patients (defined as GCS <9) should be anaesthetised and intubated endotracheally. The most important argument for endotracheal intubation is the prevention of hypoxaemia which would cause further secondary brain damage. This is usually caused by inadequate ventilation due to reduced consciousness as well as secondary to aspiration following diminished protective reflexes. While some studies suggest less favourable outcomes after prehospital intubation following TBI, it has been shown that this is largely due to a higher rate of failed intubations. A prospective randomised controlled trial (RCT) compared the neurological outcome of patients with severe TBI who were intubated by paramedics to that of patients who were primarily transported to the hospital for rapid sequence induction (RSI) by physicians in the emergency department. Prehospital endotracheal intubation performed by paramedics was successful in 97% of cases. The instrument used to determine the global disability and recovery was the Glasgow Outcome Scale-Extended (GOSe) as seen in table 2. In this study, the mean GOSe of patients intubated prehospitally was 5 (interquartile range

1-6) compared to a mean of 3 in patients who were intubated at the hospital (interquartile range 1-6) six months after the injury, which suggests a significantly better outcome when patients are intubated early ($p>0.01$). The study also reviewed the proportion of patients with favourable outcomes, defined as GOSe 5-8, after six months in both groups. In the group with prehospital RSI this included 80 out of 157 patients (51%) versus 56 of 142 (39%) in the hospital RSI group (risk ratio [RR], 1.28; 95% confidence interval, 1.00-1.64; $p = 0.046$). (8,23,24)

GOS 5-point	GOSe 8-point	Domain	Criteria
1. Dead	1. Dead	-	-
2. Vegetative State	2. Vegetative State	Consciousness	-
3. SD	3. Lower SD	Function at Home	Inability to take care of themselves for 8 hours
	4. Upper SD	Function at Home Function outside of Home	Inability to take care of themselves for 24 hours OR Unable to shop OR travel
4. MD	5. Lower MD	Work/Study Social and Leisure Family and Friends	Unable to work/study OR Unable to participate OR Constant Problems
	6. Upper MD	Work/Study Social and Leisure Family and Friends	Reduced capacity to work OR Less Participation OR Frequent Problems
5. Good Recovery (GR)	7. Lower GR	Social and Leisure Family and Friends Symptoms	Slightly less Participation OR Occasional Problems OR Some affecting daily life
	8. Upper GR	-	No Problems

Table 3 Glasgow Outcome Scale extended (GOSe) – a tool to assess neurological outcome and recovery of patients after TBI. The categories organised in a hierarchy and assigned accordingly. SD, sever disability; MD, moderate disability. Adapted from Wilson L. et al. (23)

It is advised to aim for normoxaemia (PaO_2 >60 mmHg) and normocapnia ($PaCO_2$ 35-45 mmHg) with regard to ventilation, oxygen saturation of <90% should be avoided in order to prevent further brain damage following hypoxaemia. Furthermore, in intubated patients with controlled ventilation a moderate positive end-exspiratory pressure (PEEP) of 5-8 mbar

should be applied to avoid atelectasis. Higher PEEP values are to be avoided as they lead to intrathoracic pressure changes and a high intrathoracic pressure causes diminished blood return from the brain to the heart via the jugular veins, therefore possibly raising the ICP as well. This effect however can be counteracted by elevating the patients head 30°, which can lead to a reduction of the MAP of 10 to 15 mmHg within the brain. (5,8,12)

Blood Pressure

In adults suffering from TBI it is recommended to aim for normotension with a systolic blood pressure (SBP) of ≥ 90 mmHg (Grade of Evidence: B). While it is not possible to conduct prospective RCT trials examining the effect of hypotension and hypoxia in TBI due to ethical reasons, retrospective studies have reported notably poorer overall treatment outcomes in patients who were subjected to either. In more detail, a study using data from the Japan Trauma Data Bank examined a total of 34 175 patients over the age of 18 years who suffered severe TBI. It was demonstrated that a prehospital SBP <110 mmHg significantly increased in-hospital mortality (adjusted OR 1.52, confidence interval 95%: 1.39-1.65). However, due to side effects of intensive therapeutic interventions, increasing blood pressure should not be initiated without careful considerations. The most preferable blood pressure values are however difficult to determine due to the fact that studies often consider patients with different accompanying. For instance, in the case of haemorrhagic shock studies have suggested that permissive hypotension with SBP targets ranging from 50mmHg to 70 mmHg and MAPs of ≥ 50 mmHg provide a survival benefit compared to control groups with higher blood pressures. Permissive hypotension, also known as hypotensive resuscitation, is a strategy in the management of severe trauma and refers to limited repletion of volume and accepting the consequentially lower MAP than under normal circumstances. When there is more aggressive fluid repletion there are two main issues in hypovolaemic shock. On the one hand, by infusing a large amount of non-blood products the remaining blood components, including factors crucial to coagulation, are diluted, which may in turn result in a disruption of the coagulation response. On the other hand, by increasing the cardiac output through volume infusion, the MAP also rises. This in turn inhibits peripheral vasoconstriction leading to further blood loss. (8,25-27)

Intracranial Pressure

When an increased ICP is suspected, particularly combined with signs of transtentorial herniation, the following protocols can be applied in the early phase of treatment: hyperventilation, hypertonic saline solutions and mannitol. (8)

The effect of moderate hyperventilation on the ICP is based on the physiological effects of hypocapnia on CBF. In damaged brain areas, autoregulation cannot take place due to anaerobic metabolism and lactic acidosis, leading to persisting vasodilation and vasoparalysis. Thus, hypocapnia leads to a paradox reaction in the oedematous parenchyma leading to more perfusion in the affected region. This is referred to as “inverse Steal-Syndrome” or “Robin-Hood Phenomenon”. Furthermore, vasoconstriction in the remaining areas of the brain lowers the intracranial blood volume and therefore the ICP and lactic acidosis is compensated slightly via respiratory alkalosis. (12)

Mannitol and hypertonic saline solution are both osmotic agents that may reduce ICP and improve brain prefusion. Additionally, mannitol is a scavenger of free radicals, expands plasma volume and can improve oxygen-carrying capacity. (5,8)

Others

In the case of perforating head injury, the object should not be removed but rather fixed in place and, if necessary, shortened for transportation of the patient. The object could be tamponing injured blood vessels and its removal may facilitate ICH. The removal should therefore take place under surgical conditions with the immediate possibility to stop bleeding from the injured tissue.

Any teeth that have been knocked out or any fragments should be kept moist and taken to the hospital for replantation. (8)

In critical ill patients there is often concurring hyperglycaemia, which can also be observed in patients with TBI. It is assumed that hyperglycaemia is the result of a stress response of the body after TBI and is linked to higher mortality and morbidity. Some studies observed that there was an association between elevated glucose levels and severity of TBI (measured with GCS) and the occurrence of coagulopathy. Therefore, insulin drips may be required to reduce hyperglycaemia (target 100-180mg/dl or 5.55 to 9.99mmol/l) and potentially contribute to better outcomes. (28,29)

Another factor that can contribute to a worse neurological outcome is hyperthermia due to elevation of metabolic demand and glutamate release and should therefore be treated in order to achieve normothermia. There is limited evidence for the therapeutic use of hypothermia in TBI and it can hence not be recommended as a standardised therapy.

Furthermore, the possibility of additional spinal injuries during transportation should be considered and the patient's position and mode of transportation adjusted accordingly. Finally, epileptic seizures should be treated with anticonvulsive medications. (5,8)

1.1.4.2 Intrahospital Therapy

Within the hospital, the same therapy targets as mentioned above apply with the main goal of limiting secondary brain injury and establishing the best possible conditions for brain tissue to heal. Additionally, it is recommended to obtain a CT scan of the whole body in polytraumatised patients, including a native cranial CT. In case of deterioration of neurological function, it is advised to repeat cranial imaging since intracranial bleeding can be delayed or increase over time.

Traumatic brain bleeds as well as depressed fractures causing mass effect should be surgically decompressed depending on the patient's general condition (such as age, pre-existing medical conditions and brain atrophy) and the severity of the injury.

In the case of TBI with stable neurological condition and no mass effect it is possible to proceed in a conservative manner. In this case it is however required to monitor the patients very thoroughly using clinical and radiological findings and surgical decompression should be performed if there is further deterioration. Since clinical examination is limited in unconscious and sedated patients, it is recommended to monitor the ICP invasively using a ventricular probe. This also permits direct treatment of elevated ICP by draining CSF from the ventricles.

Another highly effective method of reducing ICP is a decompressive craniectomy, which is often necessary due to the development of (secondary) brain oedema with a delay of several days after the initial trauma. (8)

1.1.5 Complications

There is a wide range of possible complications after TBI, some of which are more likely to occur in the early phase and some usually occur later in the rehabilitation period.7

1.1.5.1 Early Complications

Every open head injury bears the risk of a bacterial contamination of the wound and meninges, which can generate a number of infections such as meningitis, abscess and empyema. Nonetheless, studies have failed to prove a clear benefit of administering prophylactic antimicrobial substances in TBI.

As mentioned before, it is possible to suffer from epileptic seizures after TBI which may over time progress into posttraumatic epilepsy.

Following severe head trauma, the circulation of the CSF can be disturbed and provoke a dilation of the cerebral ventricles and hydrocephalus. This can however be prevented and treated by placing an external ventricular drain.

Other possible complications include disruptions of electrolyte balance, mostly because of syndrome of inappropriate antidiuretic hormone (SIADH) secretion and hormonal disruptions secondary to insufficiency of the pituitary gland. These hormonal disruptions can persist long after the initial trauma necessitating the substitution of deficient hormones. (6)

1.1.5.2 Long Term Complications

A liquor fistula can be the result of a fracture of the skull base and opening of the subarachnoid space, clinically manifesting as the leakage of CSF through nose, mouth or ear. The lowered ICP due to the loss of CSF can in turn present as orthostatic headache. The diagnosis is based on radiological findings in CT and MRI. Therapeutically, a surgical closure of the fistula should be performed.

An untreated fistula may be a passageway for bacteria and the origin of meningitis and cerebral abscesses (most commonly caused by Streptococcus pneumoniae) years after the injury.

Depending on the location of the main neurological injury, TBI can lead to specific neurological deficits as well as lesions of cranial nerves. Focal deficits are highly variable, for instance damage to the cerebellum could present as ataxia, while lesions of the diencephalon may result in SIADH. With regard to the cranial nerves, the most common complication is anosmia brought on by damage to the olfactory nerve, which persists in up to 2/3 of the affected individuals. Other frequently damaged cranial nerves are the optic, oculomotor and facial nerves, resulting in visual disturbances, paresis of the eye muscles and facial palsy.

In 80% of patients with posttraumatic epilepsy, seizures start within the first two years after TBI. The seizures can range from focal to secondary generalised and primary grand-mal epilepsy.

There are also numerous neuropsychological deficits (such as organic brain syndrome and posttraumatic encephalopathy) and changes in character or personality caused by TBI, which

can be the most challenging long-term effects of TBI for the patients and their professional and social environment. The symptoms may include fatigue impairment of memory, and reduced ability to focus. As a result, it can be challenging for affected people to execute complex tasks or to navigate complicated situations. Changes in personality, for instance irritability and apathy, lead to challenges in their everyday life.

The prognosis of TBI depends on the severity of the trauma. Mild injuries usually heal without any residual deficits, in moderate TBI there is a chance that deficits can regress completely or only leave little residuals. In severe TBI however, neurological and neuropsychological deficits of varying severity are to be expected if the patient survives the injuries. (6,30)

1.2 Coagulation

Haemostasis is the process of sealing up injured blood vessels in order to minimise blood loss and to re-establish the vascular integrity through the formation of a blood clot. This physiological process depends on a highly complex interaction between the endothelial cells of blood vessels, thrombocytes and a number of coagulation factors that circulate in the blood plasma or are released by injured tissues.

A resting platelet does not usually interact with the vessel wall. In response to a vascular injury, however, subendothelial collagen is revealed, which initiates the rapid adhesion, aggregation and activation of platelets. Simultaneously, tissue factor (TF) is released from the injury site, which initiates the coagulation cascade to form a more stable thrombus. Platelets and coagulation factors do influence each other to work more efficiently than they would separately. (31,32)

1.2.1 Primary Haemostasis

The adhesion of thrombocytes to newly exposed subendothelial extracellular matrix is a multistep process, mediated by their interaction with extracellular collagen, fibronectin and laminin. Stable adhesion involves tethering, rolling, activation and firm adhesion and the initial interaction of platelets with the extracellular matrix is largely defined by the local rheological condition. In lower shear conditions, such as veins, the adhesion is primarily mediated by collagen, while the von-Willebrand factor (vWF), a protein produced by endothelial cells and megacaryocytes, is crucial at higher shear rates such as in small arteries. Circulating vWF binds to collagen and unfolds in order to reveal its A1 domain, which is the

binding site of the glycoprotein Ib/IX (GP Ib/IX) on the platelets' surface. After forming bonds to the collagen, the thrombocytes need to be activated. The activation is initiated by a secretion of substances from the thrombocyte's granules, such as adenosine diphosphate (ADP), serotonin and thromboxane A2 (TxA2). Activation of platelets triggers a change in their structure, which is referred to as "viscous metamorphosis". Activated platelets change their morphology from smooth and disc-shaped to more rounded structures with long pseudopodia. This change allows the already aggregated thrombocytes to connect to each other. Through structural changes, the gylcoprotein IIb/IIIa (Gp IIb/IIIa) receptor on the platelets' outer membrane is revealed, which allows fibrinogen (Factor I in the coagulation cascade) to bind and form a white, thrombocyte- and fibrinogen-rich thrombus within the first minutes after the injury (also called aggregation). Additionally, TxA2 is a strong vasoconstrictor that further aids in limiting blood loss. (31-33)

1.2.2 Secondary Haemostasis

The white thrombus produced by primary haemostasis is not very stable and can easily be flushed away. To prevent further bleeding a more stable, red thrombus including fibrin, erythrocytes and other blood cells is formed by secondary haemostasis via the coagulation cascade. Essentially, the cascade is a series of enzyme activation events in which serine proteases activate the proteins of the next step via proteolysis. It is mainly activated through two distinct pathways, the first being the extrinsic or tissue-factor pathway, the second being the intrinsic or contact pathway. At the end of the cascade both pathways merge into the same pathway, which results in the activation of factor X to factor Xa. Activated factor X combines with factor Va, phospholipids and ionised calcium (Ca2+) and forms an enzyme complex called prothrombinase that transforms inactive prothrombin into active thrombin. (31,34-36)

1.2.2.1 Extrinsic Pathway

The key protein that initiates the extrinsic pathway is the so-called TF, also known as thromboplastin or factor III, which is the transmembrane cofactor component of the extrinsic tenase. It is expressed in the adventitial cells and through injury of the blood vessel it gets exposed to the blood. This way, TF can bind to factor VIIa, circulate in the plasma and form a complex that can activate factor X. The second substrate activated by the TF:VIIa complex is factor IX. Both, factors Xa and IXa assemble with specific cofactors (fVIIIa with fIXa and fVa with fXa), Ca^{2+} and phospholipids to continue the cascade. The factor VIIIa:IXa complex transforms large amounts of factor X into its activated form, while factor Va:Xa splits

prothrombin into thrombin. Thrombin itself has the capability to activate the factors V and VIII, which creates a positive feedback loop that sustains and enhances coagulation. The release of tissue factor pathway inhibitor (TFPI) from endothelial cells is triggered by thrombin and regulates coagulation by binding irreversibly to fXa. Subsequently a quaternary complex is formed between TFPI, fXa, fVIIa and TF which prohibits their further contribution to coagulation. As a result, any further activation of thrombin, and by extension the sustenance of the cascade, is dependent on the initial amount produced.

Additionally, thrombin cleaves fibrinogen into fibrin monomers and it activates factor XIII, which crosslinks the fibrin monomers and therefore is a key component in the formation and stabilisation of the blood clot. In the process of clot formation, circulating red and white blood cells as well as platelets are incorporated into the thrombus, giving it its description as “red thrombus”. (31,34,36-38)

1.2.2.2 Intrinsic Pathway

The intrinsic pathway is activated when factor XII comes into contact with artificial, anionic surfaces. This causes a conformational change and leads to activation of factor XII, a process also involving high-molecular weight kininogen and kallikrein. Factor XIIa then cleaves factor XI, resulting in factor XIa, which subsequently activates factor IX and continues down the same path as the extrinsic pathway (then also referred to as common pathway). It has been discovered that humans exhibiting a factor XII deficiency to not have bleeding tendencies, and as a result it is assumed that the contact pathway plays a minor role in the activation of the coagulation cascade under normal circumstances. It is however of importance when it comes to artificial heart valves, dialysis and laboratory medicine. (31,34,36,39)

1.2.3 Cell-based Model of Coagulation

While the traditional model of coagulation, involving the intrinsic and extrinsic pathways that merge to activate factor X, it fails to illuminate the role of blood cells in the process. Several factors influence the cellular component of coagulation. Firstly, blood flow is a key factor as there may be inadequate blood clotting in vessels without injury due to the lack of blood flow, while an injured vessel would be unable to form a clot if the required components are not delivered to the injury site. Secondly, there needs to be an interaction between the blood cells and clotting factors, which is facilitated by an appropriate membrane composition. Part of this composition is the asymmetry of the phospholipid bilayer in which

neutral phospholipids are located on the outside while components such as phosphatidylserine (PS) and phosphatidylethanolamine (PEA) are restricted to the inner leaflet of the membrane in inactive cells. When a cell gets injured or activated PS and PEA are relocated to the outer leaflet where they significantly accelerate certain coagulation reactions. Some other aspects are still being investigated for the relevance and nature of their contribution. This includes microparticles (MP), which are vesicles derived from surrounding cells and contain membrane surface proteins, similar to those of their parent cell. MPs are primarily derived from endothelial cells, platelets and monocytes and can therefore play a role in coagulation. (38,39)

According to newer findings, in vivo coagulation happens in two phases that overlap and require cells bearing TF and platelets. (38,39)

1.2.3.1 Initiation

Based on recent data, TF, the only relevant initiator of haemostasis, is usually found on extravascular cell membranes. When a blood vessel is injured, the flowing blood comes into contact with these TF-bearing cells and fVIIa (the sole factor routinely circulating through the blood stream in its activated form) swiftly binds to fVIIa. The TF:VIIa complex then activates even more fVII on the one hand, and fIX and X on the other hand. FXa can itself split fV into its activated form (albeit slowly) and they combine into the prothrombinase complex which splices prothrombin to produce thrombin. Once fXa dissociates from TF-bearing cells it is swiftly inactivated by either TFPI or antithrombin (AT), effectively restricting its functionality to the surface of the cell on which it was activated. (38)

1.2.3.2 Amplification

The small amount of thrombin that was produced on the surface of TF-bearing cells then disassociates and is capable of activating platelets. When thrombin binds to platelets it initiates a number of modifications to platelet function and structure: their shape is modified, the phospholipid membrane shuffled to promote blood clotting and procoagulant granules are released. Moreover, the generated thrombin cleaves fXI and fV into their active form and vWF off of fVIII (as they circulate in the blood bound together). VWf then contributes to platelet adhesion and aggregation, while fVIII is cleaved to fVIIIa by thrombin. (38)

1.2.3.3 Propagation

Granules released from the small number of activated platelets lead to further recruitment of platelets to the injured area. Due to the expression of specific ligands on their outer

membrane the platelets begin to aggregate and fXIa combines with fVIIIa located on the outside of platelets to form the intrinsic tenase complex. The main purpose of the intrinsic tenase is the swift generation of fXa directly on the membrane of platelets, which merges with fVa into the so-called prothrombinase to cleave substantial amounts of prothrombin into thrombin. The rapidly increasing amount of thrombin splits soluble fibrin from fibrinogen that will spontaneously polymerise into a insoluble matrix of fibrin strands. Another function of thrombin is the activation of fXIII that leads to cross-linking of fibrin strands, thus significantly increasing the strength and elasticity of the fibrin matrix. (38)

1.2.4 Fibrinolysis

Once the injured blood vessel has sealed up and healed, the insoluble clot is dissolved and broken down to re-establish normal blood flow. The breakdown is initiated by the local secretion of tissue plasminogen activator (tPA) by endothelial cells. Urokinase (uPA), produced by endothelial cells of the urinary tract, macrophages and monocytes is also able to instigate fibrinolysis. Compared to tPA, uPA acts mostly at extravascular locations, has a lower affinity for plasminogen and does not require fibrin as a cofactor and is therefore considered to play a smaller role in initiating fibrinolysis. Nonetheless, both, tPA and uPA operate by cleaving plasminogen into its active form plasmin that begins to degrade the fibrin mesh into fragments. When the polymers are split at the D-fragment site, the resulting degradation products are called D-dimers, which are commonly used in the laboratory to assess thrombosis and plasmin activity. Fibrin degradation products additionally play an important role in preventing further blood clotting by inhibiting the activity of thrombin.

The fibrinolytic system is, similarly to the coagulation cascade, tightly regulated by a number of inhibitors, the three most important ones being plasminogen activator inhibitor-1, plasminogen activator inhibitor-2 (PAI-1, PAI-2) and α2-antiplasmin. (31,34,37,40)

Coagulation Factor Number	Coagulation Factor Name
I	Fibrinogen
II	Prothrombin
III	TF
IV	Calcium
V	Proacclerin, labile factor
VI	Unassigned
VII	Stable factor, proconvertin
VIII	Antihaemophilic factor A
IX	Antihaemophilic factor B or Christmas factor
X	Stuart-Prower factor
XI	Plasma thromboplastin antecedent
XII	Hageman factor
XIII	Fibrin-satbilising factor
XIV	Prekallikrein (F Fletcher)
XV	HMWK (F Fitzgerald)
XVI	vWf
XVII	AT III
XVIII	Heparin cofactor II
XIX	Protein C
XX	Protein S

Table 4 Coagulation factor numbers and names; TF – Tissue factor, HMWK – high molecular weight kininogen, vWf – von Willebrand factor, AT III – Antithrombin III. Adapted from Smith SA (38)

1.3 Trauma-induced Coagulopathy

Trauma-induced coagulopathy (TIC) is a complex, biochemical response to severe trauma, involving a number of interactions between pathophysiological processes including dysregulated coagulation, a change in fibrinolysis and platelet function, systemic endothelial dysregulation and inflammatory responses. Other influencing factors also include the nature of the trauma and the resuscitative measures. Up to 30% of patients who have suffered severe trauma and injuries already display some signs of coagulopathy when admitted to the shock room and these early forms of coagulopathy are associated with a 4-fold increased mortality. Under normal circumstances there is a balance between the two opposing mechanisms of haemostasis and fibrinolysis, which ensures adequate control of bleeding following mild injuries. In response to trauma however, this balance of pro- and anti-coagulant processes is often disrupted by the so-called “vicious triad”: metabolic (lactic) acidosis caused by tissue damage, hypothermia due to exposure to a cold environment (further exacerbated by

administration of cold fluids) and coagulopathy. These three factors continuously amplify each other, leading to sustained haemorrhage and, ultimately, a depletion of coagulation factors and a higher risk of disseminated intravascular coagulation (DIC) either in the initial hours following trauma or later during hospitalisation. DIC is the intravascular activation of coagulation with loss of localisation and has to be distinguished from TIC, as this starts before the vicious triad takes effect and is therefore an aggravating component influencing the development of DIC at later stages. The pathophysiology of TIC is a complex, multifactorial process that seems to be fuelled by a number of factors, including high injury severity, prolonged episodes of hypotension, shock. Other important pathophysiological components of TIC are the further dilution of coagulation factors and blood cells through crystalloid or colloid infusion, which may be necessary as a therapeutic measure to obtain a sufficient MAP (recommended: approximately 65 mmHg) when blood products are not readily available, as well as hyperfibrinolysis. (8,41-44)

Hyperfibrinolysis is defined as a situation in which there is an excessive degradation of blood clots, resulting in severe, possibly lethal, haemorrhage. In healthy adults, fibrinogen is the most prevalent, circulating clotting factor, albeit it shows the lowest concentration of all coagulation factors in patients with significant haemorrhage. The underlying mechanisms are divers and amplify each other, ultimately triggering the loss of localisation of fibrinolysis and concomitant severe bleeding. Fibrinolysis is increased in trauma as tPA is released from endothelial cells as a result to direct injury and as a response to ischaemia. (45)

Tissue ischemia also reduces the activity of PAI-1, which, particularly in combination with elevated levels of tPA, induce the uninhibited activation of plasmin and degradation of fibrin. Additionally, higher levels of fibrin decomposition products such as D-Dimer amplify these effects, as they also inhibit the cross-linking of fibrin. Elevated levels of D-dimer have been linked to more severe tissue injuries and fibrinogen depletion and especially patients with high D-dimer and low fibrinogen were found to have a statistically significant higher mortality than the control group in a retrospective study ($p<0.001$). (45)

Another disruptive influence on coagulation is the dysregulation of thrombin activation. In early phases of haemorrhage, the generation may not be sufficient, entailing clots made up of thick, less stable fibrin strands susceptible to degradation.

While these processes mainly interfere with secondary haemostasis, platelet dysfunction, and subsequently disrupted primary haemostasis, commonly also contribute to the

development of TIC. Low platelet counts are linked to higher necessity of blood transfusions and increased early mortality, but there is an additional phenomenon when it comes to trauma patients, referred to as 'platelet exhaustion'. This is indicated by a platelet count within the normal range but a modified aggregation. This is brought on by trauma- and shock-triggered release of TF, platelet-activating factor and vWf, causing overactivation of platelets and the release of their coagulation factors. As a result, these activated, but depleted, platelets continue circulating in the body, but cannot contribute to haemostasis any further. (41-46)

TIC can be diagnosed with standard laboratory tests: complete blood count, serum electrolytes, arterial blood gas analysis and routine coagulation tests (prothrombin time, international normalised ratio, activated partial thromboplastin time) as they include all three components of the vicious triad. Moreover, fibrinogen and D-dimer levels may be measured to validate the diagnosis.

Early treatment of TIC is crucial to improve the survival rate of trauma patients. The damage control resuscitation includes permissive hypotension, avoiding an excessive administration of crystalloid infusions, as well as hypothermia and acidosis, and initiating prompt surgical intervention. The main goal in haemorrhaging patients should be euvolemia and to minimise blood loss and the resulting need for blood transfusions. It is however not clear yet which type of infusion should be administered primarily since crystalloids, colloids, Ringer's lactate solution and massive haemotransfusion all result in a further impairment of coagulation. The current status quo is to administer a bolus of crystalloid fluids (in adults up to 1 litre of isotonic solutions may be required to obtain an adequate reaction) and to start haemotransfusions if there is no sufficient reaction to the initial fluid bolus. (41-43)

1.4 Traumatic Brain Injury and Coagulopathy

While the TIC is related to extracranial injuries is usually instigated by extensive tissue damage causing hyperfibrinolysis, severe bleeding and haemorrhagic shock, as well as the vicious triad and iatrogenic haemodilution, studies have found that coagulopathy is also commonly present in patients with isolated TBI, lacking the above-mentioned initiating factors. TBI-induced coagulopathy may present itself as disseminated ICH or delayed intracranial bleeding and systemic bleeding. (2,47-49)

Since the initiating factors of TIC in patients with extracranial injuries, in particular significant blood loss and haemorrhagic shock, are not present in isolated TBI, it is assumed that TBI-induced coagulopathy follows a different pathogenic path. The onset of TBI-

induced coagulopathy is often within minutes after trauma and there may already be signs of manifest coagulopathy in the prehospital setting, suggesting it may be brought on by substances derived from the brain itself.(2)

Some elements discussed to expedite the condition are the presence of high levels of TF in the brain tissue and the interaction of plasma proteins with the brain parenchyma, usually prevented by the BBB in healthy individuals. After TBI there is a mechanical disruption of the BBB localised to the injured area and a higher permeability of the BBB in non-injured areas, due to secondary ischaemic tissue damage. As a result, there is vascular leakage into the parenchyma leading to CO2 production and the release of substances derived from the brain into circulation. Furthermore, it has been observed that TBI is associated with an early development of hyperfibrinolysis and with dysfunction of the patients' platelets. As a result of the distinctive pathogenesis, the above-described therapeutic strategies have not proven to have a consistently positive impact on the outcome of patients with TBI. (2,50)

1.5 Tranexamic Acid

TXA was first synthesised in 1962 and has since been recommended in several guidelines for various indications. The medication is typically well tolerated and any adverse drug reactions are mostly mild or moderate. Severe or serious events rarely occur, and TXA has therefore been declared an essential medicine by the World Health Organisation (WHO). The commercially available formulations of TXA are intended for oral or intravenous (IV) use but is also commonly applied topically, for example to treat epistaxis, or via nebulisation for conditions such as haemoptysis. Furthermore, usually in military settings, it can be administered via intraosseous access or as an intramuscular (IM) injection in critical patients without vascular access. (3,4,51-54)

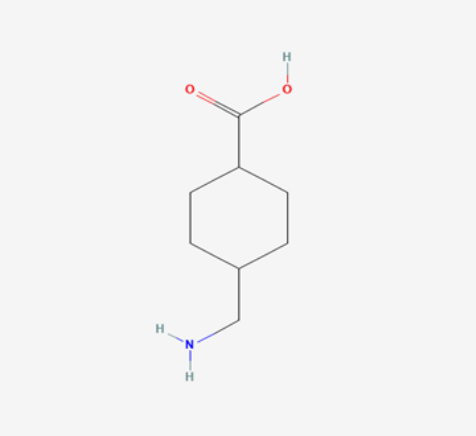

Figure 1Chemical Structure of Tranexamic Acid. Trans-Isoform of 4-Aminomethylcyclohexane-1-Carboxyacid. Oxygen atoms marked in red and nitrogen in blue. Lysin in contrast does not contain cyclohexane but an additional amino-group – 2,6-diaminohexanoic acid. (88)

1.5.1 Pharmacodynamic Properties

TXA is a synthetic molecular analogue of the essential amino acid lysin that reversibly and competitively binds to plasminogen at the lysin-binding site. Each molecule of plasminogen

contains 5 to 6 binding sites for TXA, one of them binds with hight affinity (K_D= 0.17µg/ml), the others with low affinity (K_D= 117-157µg/ml). Via this connection it interferes with the conversion of plasminogen to plasmin and nearly completely prevents the binding to fibrin and its breakdown into fragments (fibrinolysis). Figure 1 shows the chemical structure of TXA and figure 2 depicts an overview of fibrinolysis and its inhibitors, including TXA. In pharmacological studies performed on pig tissue, a TXA concentration of 10µg/ml was able to inhibit fibrinolysis by 80%, however, to achieve an inhibition of 98% a ten-fold higher concentration was necessary. Plasminogen can also be converted by other plasminogen activators (for instance tPA), TXA also hinders the binding of circulating plasmin to fibrin, leading to an inactive complex. Another function of plasmin is the activation of factor XII through the contact activation system (CAS), which is involved in the generation of bradykinin via cleavage of high-molecular-weight kininogen (HMWK) by kallikrein. Bradykinin is a vasoactive peptide causing increased vascular permeability and fluid leakage into surrounding tissue as well as vasodilation. As TXA inhibits the generation of plasmin, it subsequently counteracts the production of bradykinin and its associated effects on circulation. Studies have shown an additional modulating effect of TXA on inflammatory cytokines and activation of innate immune cells, leading to significantly lower rate of postoperative infections in cardiac patients, although all patients received prophylactic antibiotics. There are several pathways involved in the immunomodulatory effects of TXA and over a dozen plasminogen receptors have been discovered, many of which are located on monocytes and macrophages. Plasmin was found to have the capability to activate macrophages, which triggers a downward cascade of molecular pathways, ultimately resulting in the induction of proinflammatory cytokines, such as TNF- α and IL-6. It is also involved in the chemotaxis of monocytes and, increases the expression of proinflammatory cytokines via the nuclear factor ‘kappa-light-chain-enhancer’ of activated B-cells (NF-κB). Furthermore, there is a connection between the coagulation and complement system, partially through plasmin-induced cleavage of the complement factors C3 and C5 into their active form (C3a and C5a). (55-61)

In comparison to other antifibrinolytic synthetic derivatives of lysin, TXA has a plasminogen binding capacity that is up to 10-times higher. At low blood concentrations (<10mg/ml) the substance has no effect on other compounds of the coagulation system (including platelet count, prothrombin time and the levels of different coagulation factors) in healthy subjects,

but there was a prolongation of thrombin time (TT) at blood concentrations between 1 and 10mg/ml. (57)

The inhibition of fibrinolysis by TXA can be measured by reduced concentrations of D-dimer or using rotational thromboelastometry. This is a technique used to assess several steps of coagulation and fibrinolysis at the same time and provides an insight into the initiation phase, propagation, interaction of fibrin and platelets, clot stability and fibrinolysis, all with minimal time delay. At the end, a graphic representation shows the viscoelastic properties of the blood clot at all stages of development and disintegration. (62,63)

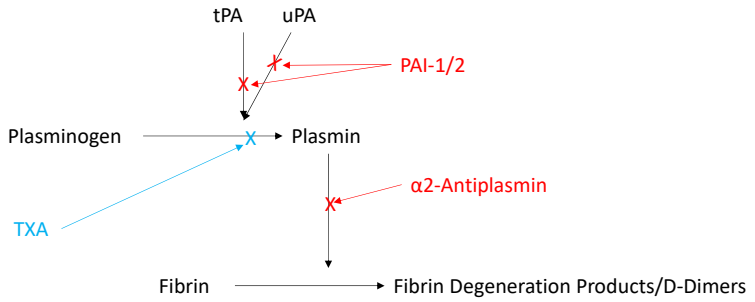

Figure 2 Fibrinolysis and Inhibitors. ; tPA: tissue plasminogen activator; uPA: urokinase plasminogen activator; PAI-1/2: Plasminogen-Activator-Inhibitor; TXA: Tranexamic Acid; Common physiologic inhibitors of fibrinolysis are marked in red, TXA is marked in blue to show their points of action. Adapted from Lier H. et al. (59)

In a study conducted throughout Switzerland using rotational thromboelastometry it was found that the infusion of TXA after trauma contributes to prolonged clot firmness and a significant reduction of hyperfibrinolysis represented by lower levels of D-Dimers, when compared to a control group. (64)

In pigs, an infusion of TXA 30mg/kg showed a difference in the activity of plasmin in varying organs and regions of the body. For instance, in plasma the maximal reduction of plasmin activity was seen 30 minutes after infusion, while the reduction peaked at 90 minutes in the liver and at 120 minutes in heart and muscle tissue. (4,52,53,60)

Laboratory Test	Normal Results	Explanation
Thrombocyte Count	140-440 x 10^9/l	Number of circulating thrombocytes, prolonged bleeding time may be observed <100x10^9/l, spontaneous haemorrhage <50x10^9/l
Quick	70-120%	Function of the (former) extrinsic coagulation path, depends on the prothrombin used by the lab; reduced in deficiency of fVII and V, disorders offo the common pathway (fX, II and fibrinogen), vitamin K deficiency and liver disease
INR	0.9-1.15	Compares measured Quick to the ISI, values irrespective of prothrombin used by the lab, otherwise comparable to Quick
aPTT	28-40 sec. (Great variation of normal range, depending on methods used)	Measures the (former) intrinsic pathway: fXII, fXI, fIX, fVIII; and common pathway; may be prolonged due to haemophilia A/B, factor deficiency (VIII, IX, XI, XII)
TT	17-24 sec.	Measures generation of fibrin from fibrinogen; reduced in fibrinogen deficiency, disorders of fibrin polymerisation; also during heparin therapy
Fibrinogen	1.8-3.5 g/l	Amount of circulating fibrinogen; decreased commonly due to hyperfibrinolysis or DIC
Bleeding Time	<6 min.	Test of global coagulation, non-specific; assessment of global risk of haemorrhage, in particular when thrombocyte count is normal

Table 5 Standard Coagulation Tests; INR: International Normalized Ratio; ISI: International Sensitivity Index; aPTT: activated Partial Thromboplastin Time; TT: Thrombin Time; Sec: Seconds; Min: Minutes; This table summarizes some of the standard laboratory tests to evaluate coagulation. More specific test may be necessary for certain diagnoses. Adapted from Braun J. et al.(65)

1.5.2 Pharmacokinetic Properties

The optimal dosage regimen of TXA for each condition is not clearly defined yet since the dosage and form of application differs in various studies and the effective therapeutic plasma concentrations have been defined by different researchers (5-10mg/l or 10-15mg/l). In one study, healthy adult subjects received parenteral and oral TXA to evaluate its pharmacokinetics. A single IV administration of 1g TXA resulted in plasma concentrations of ≥10mg/l for up to 6 hours. TXA was rapidly absorbed when administered orally or via IM injections. After oral administration the peaking plasma concentrations were reached at 2-3 hours orally and 30 minutes after IM injection. The systemic bioavailability of TXA after oral intake was found to be approximately 33%.

There was no significant impact of food intake on the plasma levels after oral administration (peak plasma concentration increased by 7% and area under the plasma concentration time curve by 16%) and the medication can therefore be applied regardless of the time since last food intake. (66)

Another study set out to determine the plasma concentrations of TXA during cardiopulmonary bypass. 21 patients undergoing this operation with a mean duration of 67 minutes (+/- 33 minutes) received an initial dose of 10mg/kg TXA over the course of 20 minutes, followed by an infusion of 1mg/kg/h TXA throughout the procedure and the initial 2 hours post-surgery. Their TXA plasma-concentrations were measured at several times during and after the infusion. At all study points the plasma concentrations exceeded 10mg/l, which is sufficient to reduce fibrinolytic activity by 80% in vitro. (67)

The binding of TXA to plasma proteins amounted to 3% and the involved proteins were almost exclusively plasminogen. The volume distribution of oral TXA was measured to be 0.39L/kg and tissue distribution was highest in liver, kidneys and lungs. There is only a small amount of metabolization of the drug: within the first 72 hours after IV administration of 1g of TXA, more than 95% of the substance were recovered unchanged in urine with a renal clearance rate of 8.2l/h and the terminal half-life of IV TXA was found to be around 2-3hours. (53)

When comparing pharmacokinetic data for IV and IM injections to orally administered TXA. It was observed that the pharmacokinetic properties of TXA are described best using a two-compartment open model with first-order absorption and elimination. In this model, age, sex and ethnicity did not appear to have a discernible influence on the pharmacokinetic properties. According to their measurements, the median time needed to reach a concentration of 10mg/l was 3.5 minutes for 1g IM application and 66 minutes for oral application of 2g TXA and the bioavailability was 1.0 and 0.47 respectively. (68)

TXA crosses the BBB, placenta and diffuses quickly into the synovia and synovial membranes, the excretion into breast milk however is very limited, only reaching around 1% of the plasma concentration.

Due to the limited metabolization of the substance, the risk of serious drug interactions is relatively low. However, there is a higher risk of thrombotic complications when TXA is administered simultaneously with certain substances such as hormonal contraception, factor

IX complex concentrates and thrombin. On the other hand, the combination with recombinant tPA may lessen the efficacy of both substances. (53,69)

1.5.3 Common Uses and Indications

1.5.3.1 Postpartum Haemorrhage

The worldwide leading cause of maternal deaths is postpartum haemorrhage, accounting for more than a quarter of childbirth related deaths. While most of these deaths occur in low- and middle-income countries, postpartum haemorrhage is also the leading cause of maternal death in high-income countries. In 2017 the WOMAN (World Maternal Antifibrinolytic) trial was published. (51)

In this trial more than 20.000 women with a clinical diagnosis of postpartum haemorrhage after vaginal delivery or caesarean section were randomly chosen to either receive a placebo or 1g of TXA intravenously (and another dose of 1g TXA or placebo if there was still active bleeding after 30 minutes or if the bleeding ceased and restarted within 24 hours of the first drug administration). The study concluded that the number of bleeding-related deaths was significantly lower in the TXA group vs the group receiving placebo (1.5% vs 1.9%; RR 0.81, CI 95%; 0.65–1.00; p=0.045), in particular if the first dose was administered within 3 hours of giving birth. There was no significant difference in the number of adverse events between the two groups. With these results it was concluded, that TXA reduces the number of maternal deaths related to bleeding without an increased risk of adverse events and should therefore be administered as quickly as possible after the onset of postpartum haemorrhage. (51,70)

1.5.3.2 Trauma

Among trauma patients haemorrhagic shock and exsanguination is the cause of death in up to 40% of cases. The Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage-2 (CRASH-2) trial, a double-blinded, RCT was conducted in 274 hospitals in 40 countries to investigate the impact of early administration of TXA on death and transfusion requirement in haemorrhaging trauma patients. (3)

The trial included more than 20.000 adult trauma patients with/at risk of trauma-related bleeding within 8 hours of injury. The patients received a loading dose of 1g TXA over 10 minutes, followed by another infusion of 1g TXA over 8 hours or placebo. The primary outcome was death within hospital in the first 4 weeks post injury (categories: bleeding, vascular occlusion, multiorgan failure, head injury and other). It was found that all-cause

mortality was significantly lower in the TXA group vs the control-group at 4 weeks post-trauma (14.5% vs 16.0%, RR 0.91; 95% CI, 0.85-0.97, p=0.0035) as was mortality due to bleeding (4.9% vs 5.7%, RR 0.85; 95% CI 0.76 to 0.96; p = 0.0077). Additionally, there was strong evidence suggesting that the effect of TXA varied according to the time of the first administration. The effect seemed to be greatest if the loading dose was given within the first hour after injury, followed by a second dose between 1 and 3 hours, whereas there seemed to be a greater risk of death due to bleeding if TXA was administered for the first time after more than 3 hours post-trauma. In conclusion, there is strong evidence that early administration of TXA reduces the mortality of haemorrhaging trauma patients while TXA after 3 or more hours is unlikely to achieve a beneficial effect. The impact of TXA on TBI will be discussed in the following chapters. The evidence for out-of-hospital application of TXA is limited. (3,4,52)

1.5.3.3 Heavy Menstrual Bleeding

Heavy menstrual bleeding is defined as a blood loss of more than 80ml per menstrual cycle, compared to the normal average loss of approximately 30ml. While a number of uterine pathologies can be the underlying cause, abnormal bleeding can also occur idiopathically. Since heavy menstruation is associated with a higher level of fibrinolytic activity, the use of antifibrinolytic drugs is suggested as an alternative to hormonal contraceptives and surgical procedures (such as endometrial resection or hysterectomy) to reduces blood loss. The efficacy of TXA for idiopathic heavy menstrual bleeding was investigated in six RCTs. The results of these trials revealed that 3.9-4.5g/day of TXA for up to 5 days every cycle consistently and significantly reduced menstrual blood loss compared to the baseline levels (control) and placebo groups. (53)

1.5.3.4 Others

The use of TXA in various surgical procedures has been evaluated over the past years in a number of studies and trials. It can be concluded, that TXA safely reduces the risk of bleeding in a number of elective orthopaedic surgeries such as knee and hip arthroplasty.

One of the most extensively researched indications of TXA is its use in cardiac surgery, including but not limited to cardiopulmonary bypass (CPB). Since patients undergoing cardiac surgery are one of the groups with the highest risk for bleeding (due to coagulopathy and fibrinolysis), the use of antifibrinolytic drugs such as TXA is now considered as a Class I recommendation (level of evidence A) in all cardiac surgeries. There is little evidence

supporting the routine administration of this antifibrinolytic drug in liver transplantation, gastrointestinal bleeding and spontaneous subarachnoid haemorrhage due to ruptured aneurisms. The application and efficacy of TXA in TBI will be discussed in the following chapters. (4,52)

1.5.4 Relevant Side Effects

Overall, TXA is a well-tolerated drug with treatment-related adverse events being relatively uncommon and serious or severe events being rare. In large RCTs the most commonly reported adverse events in were headache, nausea and vomiting, diarrhoea, dyspepsia, dizziness, back aches, numbness, dysmenorrhoea and anaemia. As mentioned before, the majority of reported events were mild or moderate and in most studies the reported incidence of adverse effects was not significantly different in the TXA groups compared to the placebo groups. (53)

One study on the use of oral TXA for heavy menstrual bleeding reported the most common side effects, with an occurrence of ≥5% in general (and overall twice as frequent as in the control group) to be headaches (55.6%), sinus and nasal symptoms (7.0%), back (23.9%) or musculoskeletal pain (5.2%), myalgia (5.2%) and anaemia (10.3%). (71)

Additional adverse effects listed in the Japanese prescribing information for TXA included drowsiness, anorexia, itching, rash and transient defective colour vision. Furthermore, hypotension can occur if IV TXA is administered too rapidly. The adverse effects in long-term treatment of heavy menstruation were very similar to those reported in short term use. (53)

Due to the TXA-induced inhibition of fibrinolysis there may be an increased risk of venous thromboembolism (VTE) following the administration of TXA. However, the significance of the effect of TXA on thromboembolic events such as deep vein thrombosis (DVT), pulmonary thrombosis (PT) and PE is not proven. The secondary analysis of a recent study examined if there was an increased risk for thromboembolic events in trauma patients after receiving TXA. The original trial included patients with at least one of the following risk factors for posttraumatic VTE: closed head injury with either ICH or suspected diffuse axonal injury, injury of the spinal cord with neurological deficit, severe chest or abdominal injury, pelvic fracture, severe venous injury that required repair, fractures of long bones of the lower extremities, shock upon hospital admission (defined as SBP<90mmHg), mechanical ventilation for >3days, placement of a femoral venous catheter or central venous

catheter or major surgical interventions on the admission day. For the secondary analysis 588 patients were excluded if key data was missing or unknown (age, sex, admission of TXA, date of clot development or discharge), TXA was administered >24h after trauma or clots were discovered on the same day as admission to the hospital. Out of the included 7331 trauma patients, 6.4% (466 patients) received TXA and were compared to non-recipients. In the TXA group 12.5% developed VTE with a mortality of 5.6%. In comparison, in the non-TXA group 4.6% of the participants developed VTE with a mortality of 1.7%. However, it must be considered that the patients receiving TXA were injured more severely than in the non-TXA group (Injury Severity Score [ISS] 16+: 69.1% vs 48.5%, $p < 0.001$) and more patients in the TXA group underwent major surgical procedures (85.8% vs 73.6%, $p < 0.001$). Additionally, patients who were treated with TXA had higher rates of transfusions (68.5% vs 23.5%, $p<0.001$) or mass transfusions (20.8% vs 2.1%, $p<0.001$) and other risk factors for posttraumatic VTE as mentioned above. After adjustment for patient demographic and clinical characteristics, it was concluded that the administration of TXA did not significantly increase the risk for thromboembolic complications (aHR 1.00, 95% CI: 0.69–1.46, $p = 0.99$) It was noted that there was a higher mortality rate in the TXA group (aHR 2.01 , 95%CI: 1.46–2.77, $p < 0.001$), but as the survival of <48h post-injury was an inclusion criterium in the original trial, the analysis of causes of death were largely due to complications and were not further elaborated on. To summarise, TXA could not be classified as an individual risk factor for VTE in trauma patients, which supports the further, careful use of TXA in early resuscitation. These findings are consistent with those of the CRASH-2 trial. (3,72,73)

2 Material and Methods

The basis for this thesis was an extensive research and review of recent publications, mainly on PubMed, concerning the application of TXA and its possible effects on the outcome of patients who have suffered TBI.

For the introductory chapter of the thesis, describing the physiologic principles of coagulation and the basic principles of TBI pathophysiology and its treatment options, a combination of medical textbooks, current treatment guidelines and research papers were used.

The main focus of the literary research was the Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage -3 (CRASH-3) trial. Subsequently, other studies conducted in a similar manner were analysed in order to compare their findings and discuss the potential risks and benefits of TXA for clinical application.

The research was conducted via PubMed, using “Medical Subject Headings” or so called MeSH-Terms. Some of the search-items used were “TXA”(MeSH) AND “TBI”(MeSH), “Antifibrinolytics”(MeSH) AND “TBI”(MeSH) and “Traumatic ICH”(MESH) AND “TXA”(MeSH) OR “Antifibrinolytics”(MeSH).

To provide an overview of the current approaches under investigation a variety of studies were included and summarised. There was some diversity in terms of the methods and outcomes of each study and with special consideration the results were compared wherever feasible.

For the discussion the statistics as provided from the trial authors were used, in some cases missing figures were calculated to supply further information on the significance of the findings. For the tables provided to compare the results concerning mortality, functional neurological outcome and progressive intracranial haemorrhage (PIH), the parameter relative risk (including 95% confidence interval and p-value) was used (or calculated when not provided by the trial collaborators) for a more consistent and comparable synopsis.

3 Results

3.1 Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage–3

The CRASH-3 study is an internationally conducted, double-blinded RCT evaluating the impact of an early administration of the antifibrinolytic drug TXA on the mortality and disability of patients with TBI. Altogether, there were approximately 10.000 patients fulfilling the inclusion criteria who were selected to receive either TXA or a matching placebo. The study intervention was the administration of 1g IV TXA followed by an infusion of another 1g dose of TXA over the course of 8 hours or a matching placebo (sodium chloride 0.9%). (74)

Endpoints

The primary outcome examined in the study was death in the hospital within the first 28 days post injury (cause-specific mortality was also determined).

Secondary outcomes included vascular occlusive events (such as myocardial infarction [MI], DVT and PE), stroke, disability, seizures, neurosurgical intervention, days spent in intensive care units and other adverse events. (74)

Inclusion, Exclusion, Randomisation

Adult patients were considered to be eligible for the trial if they had TBI in the last 8 hours TBI and showed evidence of any intracranial bleeding on a CT scan or, if no CT was available, had a GCS score of 12 or lower. Patients with significant extracranial bleeding and thus in need of immediate blood transfusion were excluded. Furthermore, even though no absolute contraindications for the administration of TXA were determined, the doctors were instructed to enrol a patient in the trial based on an uncertainty principle, meaning only if there was uncertainty as to whether the medication would be more beneficial to the patient than not receiving it.

All participants received all other standard treatments for TBI. Eligible patients were randomised and received TXA or placebo as soon as feasible. The infusions were packed into boxes of eight and numbered consecutively. When required, the lowest numbered package was collected and, provided the ampoules contained within were undamaged, at which point the patient was considered to be randomised, administered. Outcome data was

collected from all randomised patients, regardless of whether the trial treatment was completed, discontinued or not administered at all. Analysis of results was performed by intention-to-treat principle. (74)

Results

While there was no defined follow-up test, outcome data was collected 28 days after the initial treatment, at the time of death or discharge from hospital (whichever arrived first) using an outcome form. Initially, the primary outcome of the trial was in-hospital mortality within 28 days after injury, but it was adapted in November 2015 (3 years after initiation of the study) to observe the effect of TXA on head injury-related death of patients received the study drug within the first three hours after injury. This was done to permit a more stratified analysis of the effects depending on the time to treatment (≤1h, h1 to ≤3h, >3h). The tool used to assess short-term disability was the Disability Rating Scale (DRS), which quantifies the degree of neurological dysfunction in the following areas: eye opening, best verbal response, best motor response, self-care ability for feeding, grooming and toileting, cognitive function and employability. For each category points are awarded according to the level of disability, the lowest possible score being 0 and the highest 3-5, depending on the item. The points are then added up and the final score approximates the functional level: the highest possible score is 29 which equates to a completely vegetative state, while 0 represents a person with no discernible disability. It was developed to assess, track and compare neurologic disability using everyday functionality throughout treatment and rehabilitation. A more detailed overview of the DRS interpretation will be included at the end of this chapter. (75)

In total, 12737 patients from 175 hospitals in 29 countries were recruited and randomly allocated to the TXA or placebo group between 20.07.2012 and 31.01.2019. The TXA group included 50.3% (6406) of the patients, the other 49.7% (6331) were assigned to receive a placebo. Out of the recruited individuals, 98.6% (12561) did receive the first dose of the allocated treatment and a total of 9202 (72.2%) were treated in the first 3 hours after trauma. In the end it was possible to collect outcome data for 9127 participants.

The baseline characteristics were similar across the placebo and TXA groups, as well as across the groups of patients treated within 3 hours after injury and those treated after 3 hours. The participants were predominantly male (Placebo: 79%, TXA:80%) and the mean age was 43.1 years (SD 19.7) in the placebo group and 43 years (SD 19.8) in the TXA group.

Furthermore, the time since injury (Placebo: 2.9h, SD: 2.3h; TXA: 2.9h, SD: 3.2h), the GCS and the pupil reactions were comparable.

During the trial, a total of 2560 participants deceased with the mean time to death being 59 hours. Among the 9127 patients who were treated ≤3h of injury, the risk of death related to head injury was found to be 18.5% in the TXA group compared to 19.8% in the placebo group (RR 0.94; 95% CI 0.86-1.02). When the effect of TXA was stratified according to baseline GCS and pupil reaction, there was a reduction of the risk of head injury-related death in patients suffering from mild-moderate TBI (RR 0.78, 95% CI 0.64-0.95, p=0.22), whereas there was no clear evidence for improved survival rates amongst patients with severe TBI (RR 0.99, 95% CI 0.91-1.07, p=0.01). It was also noted that head injury-related mortality was lowered by TXA in patients with initially reactive pupils. Additionally, in patients with mild-moderate injury, earlier treatment was more effective than delayed treatment (p=0.005), while time to treatment showed no significant differences in patients with severe injury (p=0.73).

The impact of TXA administration on disability in survivors was also assessed, using the mean DRS scores of both groups. The DRS mean scores were comparable in both intervention groups treated within 3 hours (Placebo: 5.03, SD: 7.6; TXA: 4.99, SD: 7.6) and in patients treated more than 3 hours after injury (Placebo: 5.00, SD:7.4, TXA: 4.52, SD:7.00).

There was no evidence that the application of TXA increased the risk of stroke (RR 1.08, 95% CI 0.71-1.64), seizures (RR 1.09, 95% CI 0.9-1.33) or other adverse events. (74)

DRS Score	**Disability Level**
0	None
1	Mild
2-3	Partial
4-6-29	Moderate
7-11	Moderately severe
12-16	Severe
17-21	Extremely Severe
22-24	Vegetative State
25	Extreme V

Table 6 Interpretation of the Disability Rating Scale (DRS), Adapted from Rappaport M. et al.(75)

Limitations

There were several limitations to the trial discussed by the authors. Firstly, it was defined in the inclusion criteria, that the recruiting doctor had to be uncertain as to whether the administration of TXA would benefit the patients, but in the end nearly all patients who met the other inclusion criteria (adults, within 3 hours [originally 8 hours] of injury, GCS ≤12, any ICH on CT, no major extracranial haemorrhage) were included in the trial. The uncertainty principle was applied on the one hand for ethical reasons and to incorporate the trial circumstances more accurately into normal medical practice. Furthermore, even though the trial was one of the largest conducted on patients with TBI, the confidence intervals used in the statistical analysis were set rather wide (95%), which allows for more uncertainty about the impact of TXA. However, in light of prior evidence, the CRASH-2 trial for example, on this topic it seems unlikely that TXA did not have beneficial influence on the mortality.

The risk for DVT and PE may have been underestimated since these conditions were only diagnosed if there was radiological evidence or a positive result in the post-mortem examination. The relative risk for VTE due to TXA remains unbiased nonetheless, as the methods used to detect these complications are highly specific, meaning there are only a small number of false positives, and they are identical in the study and control group.

Another aspect to consider is the fact that patients with bilateral unreactive pupils or a GCS of 3 commonly already exhibited substantial intracranial bleedings and brain herniation and are therefore unlikely to profit from TXA. Patients presenting with unilaterally unreactive pupils were also frequently found to have developed brain herniation, which might have led to a further diminishment of the observed treatment effect. (74,76)

3.2 The “Prehospital TXA for TBI” -Trial

The Prehospital TXA for TBI trial was conducted to evaluate if the pre-hospital administration of TXA within the first 2 hours after injury leads to a preferable neurological outcome after 6 months compared to placebo. It was a double-blind, multicentre phase II RCT, including patients over the age of 15 years with moderate or severe TBI (blunt or penetrating), who were not in shock. It was carried out in 20 trauma centres and 39 emergency medical services across the United States of America and Canada. Between May 2015 and March 2017, a total of 1.063 participants were randomised, out of which 966 individuals received the assigned treatment and were included in the analysis. Recruited

patients were randomly assigned to 1 of 3 groups, each receiving a different treatment regimen. The first intervention group (bolus maintenance (BM) group, n=312, 32.3%) received a bolus of 1g IV TXA in the prehospital setting and a subsequent IV infusion of another 1g TXA over 8h upon arrival at the emergency department. The second group (bolus only (B) group, n=345, 35.7%) received a single bolus infusion of 2g TXA IV before admission to the hospital followed by a placebo and the third group (placebo group, n=309, 32%) was administered to doses of placebo in the same manner. (77,78)

Endpoints

The primary endpoint examined in the trial was the functional neurological outcome of the patients 6 months after the initial injury. This was assessed using the GOSe and subsequently categorised into favourable (moderate disability or good recovery, GOSe >4) and poor (severe disability, vegetative state or death, GOSe ≤4).

The defined secondary outcomes were 28-day mortality, DRS after 6 months, progression of ICH (>33% of the volume of subdural, epidural, and intracerebral bleedings), GOSe and DRS score at discharge, Marshall and Rotterdam scores on the initial CT scans, need for neurosurgical interventions, days free of intensive care, ventilator or hospital in general, as well as fibrinolysis at hospital admission.

Marshall and Rotterdam scores are to systems to predict mortality of patients who have suffered TBI using CT.

The Rotterdam score uses mainly CT findings and awards points accordingly and uses the sum to predict mortality. The evaluated parameters include subarachnoid or intraventricular haemorrhage (0-1 point: absent/present), epidural bleeding (0-1 point: present/absent), compression of basal cisterns (0-2 points: normal/compressed/absent) and midline shift (0-1 point: no shift ≤5mm/<5mm). (79,80)

The Marshall classification also uses CT findings to distinguish 6 groups: Diffuse injury I-IV, V – (any surgically) evacuated mass lesion, VI – non-evacuated mass lesion. (79,81)

There were further secondary outcomes defined including potential adverse effects of TXA such as the occurrence of seizures and thromboembolic events. (78-81)

Inclusion, Exclusion, Randomisation

To be included in the trial, a patient was required to be at least 15 years of age, have suffered a moderate to severe (blunt or penetrating) TBI with a GCS of 3 to 12, have at least one reactive pupil and a SBP ≥90 mmHg before being included in the randomisation process. It was also required that an IV catheter was placed pre-hospital admission to allow administration of the study drug within two hours. In case of prehospital endotracheal intubation by the emergency medical services, the providing agencies were instructed to record the GCS score before intubation and they were provided with centralised video and hands-on training to corroborate standardised GCS assessment.

A person was excluded if they did not meet all of the above characteristics or if the time of injury was unknown, the time to treatment was estimated to exceed 2 hours, there was clinical suspicion of seizure activity/acute MI/stroke, any known history of seizures/thromboembolic events/renal dialysis, cardiopulmonary resuscitation was delivered by emergency services or the person had suffered burns of >20% of their total body surface area. Further reasons for exclusion from the trial were suspected or known prisoners, suspected or known pregnancy, there was a prehospital application of TXA or any other pro-coagulant medication before the trial randomisation or patients who decided to opt-out.

The randomisation was managed by the Resuscitation Outcomes Consortium Data and Coordination Centre (ROC DCC). Recruited patients were randomly allocated to one of the 3 possible treatment groups in a proportion of 1:1:1. It was aimed to balance the interventions by the different locations, and therefore permuted blocks of different concealed sizes (blocks of 3 or 6) were used. However, since the transport destination and the responding emergency services providers varied, it was impossible to foresee the order in which the containers would be used, resulting in complete randomisation instead of permuted block randomisation. (78)

Results

Generally, the 3 groups were comparable regarding demographics, baseline anatomical and physiologic features, with the sole exception of a lower number of penetrating head injuries in the bolus only group. Across all groups the mean age was 42years. 74% of participants were male (BM: 73%; B: 74%; Placebo: 75%). The mean GCS score recorded was 8 (BM: 7.8, SD: 3.3; B: 7.8, SD: 3.3; Placebo: 7.6, SD: 3.2) and the median estimated time from injury to the administration of the study drug ranged from 40 to 43 minutes.

It was possible to obtain primary outcome for 85% (819) of included patients, with a higher rate of completed follow-up in the placebo group (87%) than in the bolus maintenance (84%) and bolus only (83%) groups. Failure to follow-up was mostly due to withdrawal from the study or the inability to contact the participants after 6 months. These patients were oftentimes injured less severely and displayed superior neurologic outcome at discharge than others.

A favourable neurologic outcome 6 months post-injury was recorded in 63% of participants in the bolus maintenance group versus 66% in the bolus only and 62% in the placebo group (adjusted odds ratio TXA combined versus placebo 1.17, 95% CI 0.96-1.58, p=0.53). All-cause 28-day mortality was examined as a secondary outcome and amounted to 16% overall (87% of which were attributed to neurologic injuries). In the groups receiving TXA as bolus maintenance and bolus only, the 28-day mortality was 14%, and in the control group 17% (adjusted difference -2.9%, 95% CI -7.0% to 2.1%, p=0.26). In some patients several CT scans were performed and progression of ICH evaluated. Amongst those treated with TXA, 16% experienced a progression versus 20% of those who received the placebo (adjusted difference -5.4%, 95% CI -12.8%-2.1%, p=0.16).

Neither the GOSe score differences (adjusted difference -0.9%, 95% CI -2.5-0.7, p=0.29) nor the mortality rates or the progression of intracranial haematomas reached statistical significant differences between treatment groups.

However, in an exploratory subgroup analysis of patients who were diagnosed with ICH at the hospital, the mortality after 28 days was significantly lower in the bolus only group compared to the other treatment arms (Bolus-Maintenance: 26%, Bolus:18%, Placebo: 27%; bolus maintenance versus placebo adjusted difference, −0.8%, 95% CI −7.0% to 8.7%, p =0 .84; bolus only versus placebo adjusted difference, −8.2% 95% CI −16.6% to −0.8%; p = 0.03; bolus only versus bolus maintenance adjusted difference, −9.0%, 95% CI −16.1% to −1.8%, p =0 .01).

In terms of adverse events, there was a larger number of thrombotic complications observed in the placebo (10%) and bolus only group (9%) than the bolus maintenance group (4%). Seizures were recorded most frequently in patients of the bolus only arm (5%, BM: 2%, Placebo: 2%), and similarly, 6% patients displaying no evidence of intracranial bleeding still presented with seizure activity in the bolus group (BM: 0%, Placebo: 2%). Other predefined adverse events were not remarkably different among the groups. (78)

Limitations

There are several limiting factors in this trial as identified by the authors. Firstly, potential bias may have resulted from differences between the groups with regard to early mortality. Patients who suffered more severe injuries but survived for a longer time in the bolus only group may have experienced a higher number of complications compared to the other groups.

Another important influence on the results is the inaccuracy in determining the time that passed between the initial injury and the arrival at the hospital. Even though those with an unclear time of injury were excluded from the trial, the call for emergency services was commonly used as a substitute for the real timepoint of injury. While this is the standard for out-of-hospital trials, a certain room for imprecision remains.

There are also some limiting factors with regard to the use of the GCS as a tool to determine the severity of injuries when enrolling patients in prehospital trials. Roughly 20% of participants exhibited a GCS of ≥13 upon assessment at the emergency department, even though only patients with a GCS<12 should have been included. As a result, the overall injury severity may have been lower than originally planned. Another limitation of using GCS is its inability to distinguish the cause of neurological impairment and as a result it initially remains uncertain whether the deficits are actually the consequence of ICH or other conditions leading to a depressed central nervous system (including intoxication and cardiovascular complications/shock). These factors might have contributed to a dilution of the actual treatment effect as only a limited number of patients suffering from intracranial bleeding were recruited.

Another potential source of bias are the 15% of participants that were lost to follow-up. These participants either withdrew from the trial post-enrolment or could not be contacted for outcome evaluation after 6 months. While prognostic data was used to anticipate and simulate the outcomes of these 15%, no definitive conclusions could be drawn, leaving the potential for bias. (78)

3.3 Impact of TXA on Haematoma Progression

Several studies have set out to investigate the influence of TXA on the progression and expansion of ICH. In this chapter, 3 additional RCTs conducted on this topic will be discussed. (82-84)

3.3.1 Effect of Tranexamic Acid on Prevention of Haemorrhagic Mass Growth in Patients with Traumatic Brain Injury

This double-blind RCT was conducted at the Shahid Beheshti University Hospital, Kashan (Iran) between 2014 and 2016. (84)

149 patients over the age of 15 years, with either isolated nonpenetrating TBI or multiple injuries and TBI, who arrived at the hospital within 8 hours after injury and displayed any kind of ICH in the initial CT (without the need for immediate neurosurgical intervention) were recruited. Patients with a disorder of coagulation, pregnancy, a serum creatinine ≥2mg/dl, major organ injuries requiring surgical intervention in the first 8 hours and those not receiving a second CT scan were excluded. The participants were subsequently separated into an intervention and a control group. The examined intervention comprised an initial dose of 1g TXA IV over 10 minutes and a maintenance dose of 1g TXA IV over 8 hours, or a matching placebo. A second CT scan was performed after 24-48 hours to evaluate the size of the haematoma, occurrence of new haemorrhage and impact of the bleeding on brain parenchyma.

74 patients were assigned to the TXA group with a gender distribution of 90.5% male and 9.5% female. The mean age in this group was 42.3 years (SD: 18.3) and the mean GCS upon arrival was 12.7 (SD: 2.83). The placebo group encompassed 75 participants (88% male, 12% female) with a mean age of 39.3 years (SD: 18.1) and a mean initial GCS of 11.65 (SD: 3.71). Therefore, the basic characteristics of the groups are similar and comparable.

In the follow-up CT the current volume of the haematoma was determined and evaluated in terms of progression, recession or no discernible change. In the TXA group 68.5% (n=50) showed a volume reduction, 20.5% (n=15) an increase and in 11% (n=8) of participants no change was noted. As a comparison, in those receiving a placebo 50.7% (n=38) displayed a reduction of the bleeding volume, 22.7% (n=17) an increase and 26.7% (n=20) no alteration. Overall, there was a statistically significant difference between the TXA and placebo (p=0.03), however when focusing solely on the expansion of bleeding volume there was no significant difference (TXA: 20.5%, mean volume change: 9.4ml [SD: 15.3ml]; Placebo: 22.7%, mean volume change: 10.2ml [SD: 10.1ml]; p=0.27; RR 0.89, 95% CI 0.55-1.74). There were also no significant differences concerning death rate (TXA: 2.7%; Placebo: 4%; RR 0.67, 95% CI 0.12-3.93, p=1) or unfavourable neurologic outcome (measured using

GOS) at discharge (TXA: 10.8%, Placebo: 17.3%; RR 0.62; 95% CI 0.22-1.46; p=0.25) and at 3 months later (TXA: 6.8%, Placebo: 14.7%; RR: 0.46, 95% CI 0.16-1.26, p=0.12).

There were no discernible adverse reactions to TXA. The most significant limitations of this trial were the small number of participants on the one hand, and the exclusion of anyone exhibiting coagulopathy on the other hand, as this is a common trauma-related complication and may be influenced by antifibrinolytic drugs. (84)

3.3.2 Tranexamic Acid for Patients with Traumatic Brain Injury: A Randomised, Double-blinded, Placebo-controlled Trial

Another study that was conducted in Thailand between October 2008 and August 2009, including a total of 238 participants examined the influence of TXA on progressive intracranial haemorrhage (PIH). (82)

Patients older than 16 years with moderate to severe TBI (defined as GCS of 4 to 12) who received a cranial CT scan within the first 8 hours after trauma and were not in need of immediate surgical care were recruited. Signs of coagulopathy, medications affecting coagulation or a serum creatinine exceeding 2mg/dl as well as pregnancy were grounds for exclusion from the study.

The primary outcome, PIH (characterised by new ICH, an expansion of prior bleedings by 25% or more in length/width/height and increase of midline shift exceeding 1mm or an increase in basal cistern in the follow-up CT), was investigated with a second CT scan performed after 24 hours (± 8 hours). The scans and any tangible changes were assessed by 2 distinct and independent neurosurgeons. Secondary outcomes included death, neurologic function at discharge (using GOS), necessity of blood transfusion or neurosurgical intervention and thromboembolic events such as MI, stroke, DVT and PE.

The planned intervention in this trial was the infusion of 1g TXA over the course of 30 minutes as a loading dose, followed by another 1g infusion over 8 hours or a matching placebo.

Out of the 238 participants, 120 (50.4%) were allocated to receive TXA and 118 (49.6%) a placebo. Between the groups there were no significant divergences in baseline characteristics such as age (TXA: 34.8 years, SD 16.0; Placebo: 34.1 years, SD 15.3), predominantly male

gender distribution (TXA: 86%; Placebo: 91%), time since injury (TXA: 6.6 hours, SD 1.69; Placebo: 7.1 hours, SD 1.29) as well as their GCS and findings on the initial CT.

The analysis was performed using an intention to treat principle and showed PIH in 18% (n= 21) of patients in the TXA group versus 27% (n=32) in the placebo group, which did not amount to a statistically significant difference (RR 0.65, 95% CI 0.40-1.05, p=0.25). There was also no statistically significant difference between the two groups concerning the risk of all-cause mortality (TXA: 12%, Placebo: 14%; RR 0.69, 95% CI 0.35-1.39) or unfavourable neurologic outcome (TXA: 18%, Placebo: 23%; RR 0.76, 95% CI 0.46-1.27). No adverse events (stroke, PE, DVT, gastrointestinal bleeding) were reported in the TXA group.

Similar to Fakharian E. et al. (84) an important limitation of this trial was the exclusion of patients showing evidence of coagulopathy. Furthermore, the impact of other injuries on TBI in patients suffering multiple traumatic injuries was not examined and thus the real effect may have been overshadowed. (82)

3.3.3 The Effect of Tranexamic Acid in Traumatic Brain Injury: A Randomised Controlled Trial

In 2014 this single-blinded, RCT was carried out at the emergency department of Vali-Asr Hospital in Iran. (83)

Patients were recruited to the trial if they were older than 15 years of age, had suffered acute traumatic ICH with a volume of <30ml (based on CT scans) and were within 2 hours of trauma. Reasons for exclusion were GCS <8, unknown time since injury, a haematoma exceeding a volume of 30ml, injuries requiring surgical interventions, any focal neurological deficit, midline shift caused by CO, application of TXA in the previous 14 days or any other congenital/acquired haemostatic disorders, presence of subarachnoid haemorrhage, serum creatinine levels >2mg/dl, history or evidence of current thromboembolic events, pregnancy, hypersensitivity to TXA and a history of colour blindness or other vascular ophthalmological disorders.

In total, 80 participants were enrolled in the trial and 40 were allocated to each of the 2 study groups. One group received a bolus of 1g TXA over 10 minutes and a subsequent infusion of 1g TXA over 8 hours, while the other group received placebo. There were 32 male participants (80%, 8 female participants = 20%) in the TXA group with a mean age of 35.4

years (SD: 14.6 years) and 28 male participants (70%, 12 female = 30%) in the placebo group, the mean age being 36.2 years (SD: 14.9 years). The mean volume of ICH on the initial CT scan performed upon arrival at the hospital was 21.6ml (SD: 5.37ml) in the TXA group compared to 22.2ml (SD: 4.9ml) in the control group. After 48 hours, a follow-up CT was performed to measure the extent of increase in the volume of the haemorrhage.

While there was progression of ICH volume in both groups (TXA after 48h: 23.3ml, SD: 6.4ml; Placebo: 26.5ml, SD: 6.4ml), it was smaller in patients receiving TXA ($p=0.04$). This phenomenon was also observable in the mean volume expansion (TXA: 1.7ml, SD: 9.7ml; Placebo: 4.3ml, SD: 12.9ml; $p <0.001$).

There are however some limitations to the findings of the trial. Firstly, only a small number of participants was recruited. Secondly, the trial was conducted as a single-blind trial, which leaves more possibilities for potential bias. Lastly, there were no examinations to screen for coagulopathy, which can be used to approximate the potential impact of TXA on the injuries. (83)

4 Discussion

The aim of this thesis was to identify possible beneficial effects of TXA on mortality and functional neurological outcome of patients with TBI. There is strong evidence supporting the use of antifibrinolytic medications (for example TXA) for patients with severe haemorrhage and coagulopathy. (3)

In contrast, since the underlying mechanisms of coagulopathy related to TBI seem to differ from typical TIC, currently available data and expertise is insufficient to provide clear and generalised recommendations for coagulopathy related to TBI. Based on the current results of the included studies, it was not possible to prove a significant decrease in the mortality of patients with TBI through the application of TXA. Nonetheless, there was some evidence suggesting benefits of TXA for specific patient groups, namely those with mild-moderate TBI and in particular when the application was soon after injury. (74) Furthermore, there were no statistically significant improvements accredited to the application of TXA with regards to favourable neurologic outcome (usually defined as a GOSe score >4) at different times after injury. One trial showed a significantly smaller mean expansion of ICH when TXA was applied compared to the placebo while the other trials were not able to find any statistically significant influences on PIH. (83)

In previous trials, TXA was found to be generally well-tolerated with only few side effects or adverse reactions. This can also be concluded from the trials analysed in this thesis. While slight disparities in the rates of thrombotic complications and seizures were noted when comparing two different dosage regimens of TXA with a control group in one trial (78) generally speaking no increased risk of vascular occlusive events (for instance stroke, MI, DVT and PE), seizures or other adverse events were reported among patients treated with TXA.

4.1 Mortality

Among the studies included in this thesis, 3 trials examined the mortality rate of participants in their analysis as either the primary or a secondary outcome. The results can be found in the table at the end of the chapter.

In the CRASH-3 trial (74) a reduction of head injury-related mortality was found in the group receiving TXA. The effect was even more evident in subgroup analyses stratified according to baseline GCS, pupillary reaction and time to treatment. It was found that

patients with mild-to-moderate TBI seemed to benefit more than those with more severe injuries (mild-moderate RR 0.78, 95% CI 0.64-0.95, p<0.001; severe RR 0.99, 95% CI 0.91-1.07). It was further concluded that the medication is significantly more effective in less severely injured patients (p=0.007), in particular when administered as early as feasible (p=0.005). (74)

Rowell S. et al. (78) analysed mortality rates as a secondary outcome, comparing two different dosage regimens of TXA (2 separate infusions of 1g TXA each (=bolus maintenance group) versus a single 2g TXA bolus) to a placebo. While the reduction of mortality between the 3 groups was not statistically significant, there were evident changes. In an exploratory subgroup analysis of patients who were diagnosed with ICH at the hospital, there was a lower mortality rate in the bolus group (18%) as compared to bolus-maintenance (26%) or placebo (27%). The OR when comparing the bolus and the bolus-maintenance group was 0.5 (95% CI 0.27-0.94, p=0.07) and 0.5 (95% CI 0.26-0.95, p=0.17) in the comparison of bolus versus placebo. While these reductions were not statistically significant, they are apparent. As a contrast, the OR of bolus-maintenance versus placebo was 1.0 (95% CI 0.54-1.87). (78)

In the trial conducted by Fakharian E. et al. (84) there was a notably lower mortality rate in both, study and control group compared to the other included studies (TXA: 2.7%, placebo: 4%). The authors however did not elaborate any further on possible reasons for this. There was no significant difference in the mortality between the groups: RR 0.67 (95% CI 0.12-3.93). (84)

The fourth trial examining the difference in mortality was performed by Yutthakasemsunt S. et al. (82) in Thailand. They found, that TXA did reduce the risk of all-cause mortality compared to the placebo (TXA: 10%, Placebo: 14%), yielding a RR of 0.69 (95% CI 0.35 – 1.39). (82)

Even though it was not possible in any of the trials to accredit TXA with a statistically significant reduction of mortality in patients with TBI, there were some promising findings. Generally, those who seemed to benefit most from TXA were patients with mild to moderate injuries and reactive pupils, who received the drug as soon as possible (for instance within 3 hours in the CRASH-3 trial), while those with severe TBI showed very few benefits. It was furthermore observed that the application of TXA to patients who were diagnosed with ICH reduced their risk of death. Considering these findings, as well as the fact that the exact

mechanisms of TBI-induced coagulopathy are currently not fully understood, the routine application of TXA for TBI cannot be generally recommended.

It is however important to consider that these studies, while generally examining similar outcomes and interventions, differ from each other in some critical aspects. These divergences include for instance the number of recruited individuals (ranging from 238 to nearly 13 000) and the time to treatment (ranging from application of TXA in the prehospital setting up to 8 hours after injury). This leads to results that can be challenging to compare alongside each other, making it difficult to draw meaningful conclusions. (74,77,78,82-84)

Study	**TXA**	**Placebo**	**Statistical Result**
CRASH-3 collaborators 2019 (74)	n = 4631 18.5%	n = 4514 19.8%	RR 0.94 95% CI 0.86-1.02
Rowell S. et al., 2020 (78)	n = 657 14%	n = 309 17%	RR 0.82 95% CI 0.51 to 1.13
Fakharian E. et al., 2018 (84)	n=74 2.7%	n=75 4%	RR 0.67 95% CI 0.12 to 3.93
Yutthakasemsunt S. et al., 2013 (82)	n=120 10%	n=118 14%	RR 0.69 95% CI 0.35 to 1.39
Jokar A. et al., 2014 (83)			

Table 7 Comparison of study outcomes – Mortality in absolute (n) and relative (%) numbers and resulting relative risk with 95% confidence interval

4.2 Functional Neurologic Outcome

All of the examined studies, with the exception of Jokar A. et al., (83) included some form of analysis of functional neurologic outcome of participants. A summary of these results is depicted in the table below. There are a number of tools and scales to evaluate disability after TBI. In this paper three scores, namely GOS, GOSe and DRS, were used to assess and compare the obtained results. The different scales can be challenging to compare, as they all yield different numbers and are often used at different stages of treatment. However, the scores are commonly dichotomised into favourable and unfavourable outcome, facilitating their comparison. Another difficulty is the lack of an official value for classifying favourable or unfavourable outcomes, and in different trials the GOSe cut-off value for favourable

outcome ranged from 3 to 8 points. These discrepancies complicate the comparison of results considerably. In the majority of trials reviewed in this paper, GOSe or its predecessor GOS was used, while the CRASH-3 collaborators (74) relied on DRS as secondary outcome. (75,85,86)

In the CRASH-3 trial no significant difference was found in the mean DRS scores of the TXA and placebo group for patients treated within 3 hours or after 3 hours. In either group, the mean DRS was determined to be around 5 points, which can be equated to a moderate level of dysfunction. (74,75)

Rowell S. et al. (78) used the GOSe to objectify neurological function after TBI and defined a GOSe >4 as a favourable neurologic outcome in their trial. Among all participants who received either dosage regimen of TXA, 64% (bolus-maintenance: 63%, bolus:65%) recovered with a favourable outcome 6 months post injury, while 62% of those who were allocated to receive the placebo recovered with a favourable outcome. These differences were not statistically significant. In an exploratory analysis of subgroups of patients who showed evidence of ICH upon hospital admission, the rate of GOSe scores >4 were highest in the bolus-only group (bolus: 55%, bolus-maintenance: 47%, placebo: 50%) with an adjusted OR of 1.34 (95% CI 0.79 – 2.29) compared to placebo and 1.68 (95% CI 1.0-2.82) compared to the bolus-maintenance regimen. This suggests an association of a 2g bolus of TXA with a favourable neurologic outcome in patients with traumatic ICH.

Additionally, the DRS was obtained after 6 months, which did not show any significant differences between patients treated with TXA or placebo (mean DRS TXA: 6.8, placebo: 7.6; adjusted difference −0.9, 95% CI −2.5 to 0.7; p = 0.29). It is however imperative to heed the 15% of participants lost to follow-up as they were generally injured less severely and showed superior outcomes at discharge, potentially distorting the trial results. (78)

The trials conducted by Fakharian E. et al.(84)and Yutthakasemsunt S. et al. (82) used the original GOS. Neither study was able to prove a statistically significant increase in the rate of favourable neurologic outcome at hospital discharge, accredited to TXA admission. Nonetheless, Fakharian E. et al. also obtained GOS scores 3 months post discharge, which showed a considerably lower amount of unfavourable neurologic outcome among the TXA group, RR 0.46 (95% CI 0.16 – 1.26). (82,84)

Study	TXA	Placebo	Statistical Result
CRASH-3 collaborators 2019 (74)	DRS 4.88 SD 7.6	DRS 5.03 SD 7.6	Adjusted difference -0.04
Rowell S. 2020 (78)	Unfavourable neurologic outcome at 6 months (GOSe) 35%	Unfavourable neurologic outcome at 6 months (GOSe) 38%	RR 0.93, 95% CI 0.75 to 1.11
Fakharian E. 2018 (84)	Unfavourable neurologic outcome Discharge/3 months (GOS) 10.8%/6.8%	Unfavourable neurologic outcome Discharge/3 months (GOS) 17.3%/14.7%	RR discharge/3 months 0.62, 95% CI 0.22 to 1.46 / 0.46, 95% CI 0.16 to 1.26
Yutthakasemsunt S. 2013 (82)	Unfavourable neurologic outcome at discharge (GOS) 18%	Unfavourable neurologic outcome at discharge (GOS) 23%	RR 0.76 95% CI 0.46 to 1.27
Jokar A. 2014 (83)			

Table 8 Comparison of study outcomes - Functional Neurological Outcome assessed using Disability Rating Scale (DRS), Glasgow Outcome Scale (GOS) and Glasgow Outcome Scale (GOSe) including relative risk and 95% confidence interval; SD: Standard Deviation;

4.3 Impact on Progressive Intracranial Haemorrhage

Another relevant aspect of TXA for the treatment of TBI is its potential to reduce or impede the progression of ICH. A synopsis of the trial results is included at the end.

In the study performed by Rowell S. et al. (78), 49% (n=154) of participants in the bolus-maintenance group, 52% (n=178) of the bolus-only group and 48% (n=148) of the placebo group were evaluated for PIH. In the bolus-maintenance category 17% showed a progression (mean initial bleeding volume of 9.8 mL, SD 20.8), 15% of those receiving only one TXA bolus (mean initial volume of 9.3 mL, SD 22.9), while in the placebo group 20% had progressive bleeding (mean initial volume of 8.0 mL, SD 16.5).

When comparing the results of participant treated with either regimen of TXA and those who received a placebo, the OR is 0.69 (95% CI 0.39 – 1.20, p=0.19) and therefore not statistically significant. (78)

Fakharian E. et al. (84) and Yutthakasemsunt S et al. (82) came to similar conclusions in their trials. In the first study, 20.5% of patients treated with TXA showed PIH, compared to 22.7% in the control group, RR0.89 (95% CI 0.55-1.74). It is worth noting, that there was a larger proportion of patients who were found to have a volume reduction or a steady ICH volume in the follow-up CT after 48 hours after being treated with TXA (ICH volume reduction: TXA: 68.5%, placebo: 50.7%; no change in ICH volume: TXA: 11%, placebo: 26.7%, p=0.03 for the comparison of all three croups). The latter trial described PIH in 18% of patients receiving TXA versus 27% of patients who received the placebo, RR 0.65 (95% CI 0.40-1.05), approaching statistical significance. (82,84)

Jokar A. et al. (83) found that expansion of ICH was significantly lower in the TXA group. The initial mean ICH volume was 21.6ml (SD 5.37ml) in the TXA group and 22.2ml (SD 4.9) in the control group (p=0.83). After 48h hours there was a mean expansion of ICH of 1.7ml = 7.9% (SD 9.7ml) in the TXA group, compared to 4.3ml = 19.4% (SD 12.9ml). In other words, the absolute expansion of ICH was 2.6ml, and the relative expansion 2.45-fold greater in the control group (p<0.001). (83)

Study	TXA	Placebo	Result
CRASH- 3 collaborators 2019 (74)			
Rowell S. 2020 (78)	n=332 16%	n=148 20%	RR 0.79 95% CI 0.38 to 1.20
Fakharian E. 2018 (84)	n=74 20.5%	n=75 22.7%	RR 0.89 95% CI 0.55 to 1.74
Yutthakasemsunt S. 2013 (82)	n= 120 18%	N=118 27%	RR 0.65 95% CI 0.40 to 1.05
Jokar A. 2014 (83)	Mean volume expansion 1.7ml=7.9% SD 9.7ml	Mean volume expansion 4.3ml=19.4% SD 12.9ml	Adjusted difference -2.6ml p<0.001

Table 9 Comparison of Study Outcomes – Progressive Intercranial Haemorrhage in % or absolute in millilitres (ml), including relative risk and 95% confidence interval; SD: standard deviation

4.4 Limitations

All of the trials reviewed in this thesis had the common objective of examining the impact of TXA on TBI outcome, there were however great variabilities in terms of the study designs. On the one hand, there was a substantial range of the number of enrolled participants, the largest RCT comprising nearly 13000 individuals, while the smallest trial was conducted on 80 patients. Another diverging aspect was the timing of the TXA application. Four of the studies examined the effect when TXA was applied at the hospital, usually within 8 hours of injury, while Rowell S. et al. (78) set out to administer TXA in the prehospital setting, no later than 2 hours after trauma. When it was realised, that the treatment effect of TXA was greater when applied early, the primary outcome of the CRASH-3 trial (74) was adapted to only include patients that received TXA within 3 hours of trauma, essentially rendering the data collected before then with little to no use. Lastly, the primary outcomes investigated also varied greatly. The CRASH-3 collaborators mainly focused on mortality, while considering neurological functionality (among others) as a secondary outcome. Rowell S. et al. however directed their main attention on functional neurological outcome after 6 months.

The other three trials centred around the potential benefits of TXA on progression of intracranial bleeding. This heterogeneity made it challenging to summarise and compare the results. Another complicating factor the variety of different tools and scales used by different authors to assess neurological function. As a result, no general statements could be made. (74,78,82-84)

It is practically impossible to isolate the impact of TXA in these studies, as there are no specification with regard to other treatments participants may have received due to TBI or concomitant injuries. There was also no information on the standard procedure for treating TBI at the different trial locations, making it difficult to evaluate the potential influence of other conditions and medications. For example, factors such as hypotension can dramatically exacerbate secondary injury in TBI, while permissive hypotension may be desired in haemorrhaging patients. Subsequently, any results, statistically significant or not, should be treated with caution. (5,8,19,24-26)

4.5 Directions for Future Research

In a number of studies, some of them included in this paper, there have been promising findings supporting the benefit of TXA for with the management of TBI. (74,78,82-84)

However, most of these results did not reach statistical significance and consequently no general recommendation for TXA application can be made at this point.

When conducting further trials, it should be considered to base the design on some of the already existing, large RCTs in order to facilitate comparability. Furthermore, it would be prudent to conduct trials with patients who have suffered isolated TBI, thus potentially eliminating some of the other influencing factors. The treatment effect may be observed best if the participants are treated for isolated TBI with a standard operating procedure that is similar or identical across all participating locations.

It was evident in the trials, that patients with mild-moderate TBI, who received TXA at the earlies possible timepoint, and those with present ICH, profited the most from TXA, while the outcome in severe TBI was hardly influenced. Thus, it could be considered to include only individuals who meet these criteria in future studies. (74,83)

4.6 Conclusion

TXA has become an increasingly vital component of critical care medicine, in particular in the treatment of patients with severe bleeding. It was established that the medication can

significantly reduce all-cause mortality of haemorrhaging trauma patients, while having only a limited number of adverse events, the vast majority of which are not serious. (3)

Various studies have since set out to determine other potential indications for antifibrinolytic drugs including TBI.

The trials discussed in this thesis examined the use of TXA for patients who have suffered TBI, the main focus being placed on mortality, functional neurological outcome and PIH. While most of the results did not reach statistical significance, there were some apparent beneficial effects when TXA was administered.

Patients with mild-moderate TBI did show a significant improvement in the mortality rate when receiving TXA, compared to the control group or patients with severe TBI. It was further concluded that an early application had a stronger treatment effect. (74)

One study found, that contrary to the widely recommended application of an initial 1g IV infusion, followed by another 1g IV infusion within 24 hours, a single 2g IV bolus of TXA in patients with ICH significantly improved mortality rates. (78)

It was also observed that individuals who were diagnosed with ICH upon the first CT at the hospital, experienced a considerably reduced expansion of ICH in the first 48 hours after injury when TXA was administered. Additionally, patients who were treated with TXA had higher rates of steady or reduced ICH volumes compared to those treated with placebo. (83)

No beneficial influence of TXA on neurological outcome could be proven in any of the included studies. (74,78,82,84)

When interpreting findings from these studies it is important to consider that not all pathophysiological pathways and mechanisms involved in TBI are currently fully understood. This includes for instance the pathophysiology of TBI-induced coagulopathy, which may be a key element for the mechanism TXA influences the outcome of these patients. Additionally, patients with multiple severe, extracranial injuries and TBI may have different treatment priorities than those with isolated TBI. This is especially problematic when there is life-threatening haemorrhage, as permissive hypotension is one of the recommended measures in its initial treatment, while extended periods of low blood pressure can drastically exacerbate secondary injury after TBI. (14,19,25-27,42,50,87)

In order to make an explicit, evidence-based recommendation for or against the use of TXA for patients with TBI, more trials need to be conducted. To obtain significant and clinically

relevant data, special emphasis should be placed on the design of potential future studies. A sufficient amount of participants need be enrolled, to facilitate generalisation, while specifically including patient groups who seemed to benefit from TXA as discussed above. The conditions should be as controlled and standardised as possible, to allow for comparability of the results and to observe the treatment effect of TXA. A substantial number of centres should be included to permit this standardisation while still recruiting sufficient participants, despite the narrowed-down inclusion criteria. Additionally, similarly to Rowell S. et al. (78)the incorporation of prehospital emergency services should be considered, as this would enable an early admission of TXA when indicated.

This way it may be attainable to identify the indications and patients who could benefit the most from TXA after TBI, and to make a universal recommendation for, or against, its therapeutic use.

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