Chapter 1

Introduction

1.1 Background

Traumatic brain injury (TBI) is defined as when an external physical force causes brain disturbances or any other indications of brain damage. World-wide, around 50 million cases of TBI tend to occur every year, meaning that about half of the global population will have to experience a TBI at some point in their lives. In the United Kingdom, among individuals under 40 years old, TBI is considered one of the leading causes of death and disability. In low- and middle-income countries, the TBI cases that may increase rates of morbidity and mortality are even higher. Annually, TBI imposes a cost of approximately 400 billion US dollars on the global economy, amounting to 0.5% of the world's gross product. (Khellaf, Khan and Helmy, 2019)

The full burden of traumatic brain injury (TBI) is more than numbers of how often it happens or lives lost. A clearer picture is achieved through burden of disease measures, like years of life lost to medical/mental conditions and years lived with disability, as provided by disability-adjusted life years (DALYs) measures. According to the Global Burden of Disease (GBD) report, TBI produced a total of 8.1 million YLDs (years lived with disability) in 2016. Years of life lost has been presented in years of life lost (YLL) or its various derivatives in diverse populations/settings. In a review of sixteen European countries, it was reported each TBI related death produced almost ~24 YLLs resulting in around 160 YLLs per 100,000 all-age-ages standardized rates. Some studies have reported on the deadly and disabling effects of TBI using disability adjusted life years (DALYs). One study estimated TBI produced 20,300 DALYs in New Zealand, of which represented ~27% of all injury related health loss and ~2.4% of all causes DALYs. Of the TBI related DALYs, ~71% of them were fatal. (Maas *et al.*, 2022)

The age group of 0-19 years, which includes children and adolescents, has the second-highest number of hospital admissions for TBI. In the EU, 345 children or adolescents are admitted to hospitals for treatment of TBI every 100,000 people; indicating that there are about 184 YLLs per 100,000 people. A mild TBI affects between 1 – 2 million children and adolescents in the United States annually. Youths who have previously experienced concussion are four times more likely to have a recurrent concussion. (Maas *et al.*, 2022)

’s population is 250 million people, and it’s considered as a densely populated lower come country. In West Nusa Tenggara province, which is a densely populated region, er of patients suffering from TBI being treated in the hospitals of that region have increased due to the increase in using cars and motorbikes in recent years. Despite the increase in TBI cases in the region, there is a clear noticeable lack of data on the burden and epidemiology of TBI in Indonesia. Therefore, to minimize this burden, especially in rural and remote regions, public health and preventive medicine schemes must first understand the circumstances that lead to TBI and describe the characteristics of TBI cases. (Rosyidi *et al.*, 2019)

Based on the temporal aspect of brain injury, TBI is further classified into two categories: 1) primary injury, which results directly from mechanical forces during the initial impact, and 2) secondary injury, which is mostly caused by tissue and cell damage associated with the primary injury. The primary injury causes physiological, cellular, and biochemical events that result in a long-term secondary injury which can last from hours to years. Brain edema, a drop in cerebral perfusion pressure (CPP), and an increase in intracranial pressure (ICP) can result from secondary brain injury caused by the lack of autoregulation of cerebrovascular blood flow and impaired blood-brain barrier (BBB). (Sabet, Soltani and Khaksari, 2021)

In patients with acute cerebral edema, the elevated pressure is thought to be the cause of death. Mannitol is a frequently used medication whose ability to lower ICP has been widely recognized. Hypertonic saline and mannitol are the focus of present research as potential treatments for cerebral edema and increased ICP caused by neurological diseases. However, severe side effects like rebound cerebral edema and acute renal insufficiency are becoming increasingly obvious. (Shi *et al.*, 2020)

After TBI, glucocorticoids help in reducing brain edema and neuroinflammation, which can prevent secondary damage. A review published in 2022 emphasized the significance of glucocorticoid-dependent mechanisms in regulating inflammation, particularly in the hippocampus, a region vulnerable to post-traumatic complications like epilepsy and cognitive impairment. Although glucocorticoids are useful in controlling inflammation, high or prolonged dosages of these drugs can worsen neuroinflammation in the brain, which affects the hippocampus region. Following a TBI, this inflammation may result in long-term complications like depression, epilepsy, and cognitive impairments. (Komoltsev and Gulyaeva, 2022)

this background, the writer is interested in choosing the title about the analysis of the use ol and dexamethasone in TBI patients at Dr. Wahidin Sudirohusodo Hospital, Makassar.

1.2 Problem Formulation

Based on the previously explained background, the problem formulation of this study are is follows:

Is there a relationship between the use of mannitol and dexamethasone as therapy and the discharge outcomes of TBI patients?

1.3 Research purposes

1.3.1 General purpose

To determine the relationship between the use of mannitol and dexamethasone as therapy and the discharge outcomes of TBI patients

1.3.2 Specific purpose

1. To determine the relationship between the use of mannitol and dexamethasone as therapy and the patient age on the outcomes of TBI patients at Dr. Wahidin Sudirohusodo Hospital.
2. To determine the relationship between the use of mannitol and dexamethasone as therapy and the patient gender on the outcomes of TBI patients at Dr. Wahidin Sudirohusodo Hospital
3. To determine the relationship between the use of mannitol and dexamethasone as therapy and the drug dose on the outcomes of TBI patients at Dr. Wahidin Sudirohusodo Hospital.
4. To determine the relationship between the use of mannitol and dexamethasone as therapy and the TBI diagnosis on the outcomes of TBI patients at Dr. Wahidin Sudirohusodo Hospital.
5. To determine the relationship between the use of mannitol and dexamethasone as therapy and the type of drug administration on the outcomes of TBI patients at Dr. Wahidin Sudirohusodo Hospital.

efits of the research

Clinical benefits

- For the Hospital: Offers insights for optimizing treatment protocols, reducing side effects, and improving patient care.
- For Academia: Contributes to the knowledge base in neurosurgery and neurology, serving as a reference for students and researchers.
- For the Researcher: Enhances the researcher's understanding of the therapeutic use of mannitol and dexamethasone in traumatic brain injury patients.

1.4.2 Academic benefits

- The research expands understanding of the relationship between various factors and the use of mannitol and dexamethasone for TBI therapy, particularly at Dr. Wahidin Sudirohusodo Hospital.
- It provides valuable information for future studies on this treatment approach.

CHAPTER 2

LITERATURE REVIEW

2.1 Definition of TBI

The World Health Organization considers head trauma, or traumatic brain injury (TBI), to be, "an alteration in brain function, or other signs of brain pathology, caused by an external force." This definition excludes clinical symptoms resulting from other causes, such as, medications, alcohol and drug use, treatment of non-brain injury (e.g., systemic trauma, facial fractures, intubation), as well as non-trauma related clinical criteria such as, psychological factors, communication barriers, existing medical illnesses, or injuries by objects penetrating the head. (Lefevre-Dognin *et al.*, 2021)

Another important definition, from the Demographics and Clinical Assessment Working Group of the International and Interagency Initiative on Common Data Elements for TBI and Psychological Health Research, states that TBI is, "a change in brain function, or other signs of brain pathology, due to an external force." (Lefevre-Dognin *et al.*, 2021)

TBI can occur by various types of mechanical force to the head. Some of these forces can be, single/direct blows to the head, falls, or an action causing the brain to rapidly accelerate and decelerate within the confines of the skull. The external forces can work in isolation or in conjunction with one another. While TBI has widely recognized definitions, we must also recognize it is not a singular pathological occurrence, rather it is a multidimensional-disease process that encompasses structural and functional changes in the brain tissue. There are two stage of TBI, primary and secondary injury. (Alam *et al.*, 2020)

The primary brain injury refers to the initial physical damage to all the brain components. These components include, neurons, axon, glial cells, and blood vessels at the moment of the traumatic event. Physical damage can be focal (localized), multifocal (multiple discrete area), or diffuse (widespread effect), depending on the external force's location, direction, and magnitude. The secondary brain injury across time and is the minutes after the injurious event to perhaps months and years later. The initial trauma initiated a complex cascade of metabolic, neurochemical, cellular, and molecular processes after the trauma. The body and brain continues to undergo

eyond the event that may worsen the primary damage and negatively impact long-term tcomes. (Alam *et al.*, 2020)

2.2 Epidemiology of TBI

TBI causes a large percentage of life years with impairment and is a leading cause of death and disability globally. 50–60 million people worldwide—including at least 3.5 million in the US and 2.5 million in Europe—are impacted by a new TBI every year, according to population-based studies. Mild TBI accounts for 60–95% of cases. By 2020, TBI is predicted to rank as the third leading cause of disease burden worldwide. (Lefevre-Dognin *et al.*, 2021)

According to estimates, the annual incidence for hospitalized patients is 200–300/100,000 people, and it is likely twice as high when non-hospitalized patients are considered. In New Zealand, a population-based study that included all TBI cases—whether hospitalized or not, fatal or not—reported a higher incidence than anticipated, with a total of 790/100,000 people annually (including 749 cases per 100,000 of mTBI). As with the majority of earlier research, there was a pronounced gender effect, with men being impacted more often than women (RR = 1.77). (Lefevre-Dognin *et al.*, 2021)

The global incidence of TBI is estimated to be 69 million (95% CI: 64–74 million) cases annually worldwide. In Australia and other high-income countries (HICs), TBI is the top cause of death for people under 40. Age, sex, and ethnicity are some of the variables that affect TBI incidence rates and outcomes in Australia. It is estimated that 75–90% of TBI cases are mTBI. While the United States data shows a rate of 1.9%, Australian data shows that between 1.1% and 1.3% of all emergency department (ED) patients present with a mTBI. In as many as 50% of mTBI cases, chronic complications develop that last for years after the injury. (Hiskens *et al.*, 2023)

The following findings were reported by a study that performed a systematic review and meta-analysis of 36 studies involving over 2.5 million TBI patients: First, regardless of location, males were more likely to suffer from TBI. Second, compared to urban environments, the total prevalence of brain trauma was considerably greater in rural populations and involved more transport incidents. Third, the likelihood of a successful discharge was doubled for TBI patients from urban regions. (Chequer de Souza *et al.*, 2024)

2.3 Pathogenesis of TBI

A primary mechanism leads to TBI, such as blunt impact and rapid deceleration, that causes immediate damage to brain tissue in the form of vascular insult, neuronal shearing, disruption of the blood-brain barrier, mechanical deformation, neuronal depolarization, and axonal stretch injury. The primary injury opens the door for a more extensive and prolonged cascade of secondary injuries. (Freire *et al.*, 2023)

The secondary injury is a more progressive event characterized by cellular and molecular responses that attempt to maintain homeostasis but ultimately intensify the injury. One of the main mechanisms is excitotoxicity, an over-abundance of glutamate release. This leads to overstimulation of NMDA receptors (along with calcium influx), leading to mitochondrial dysfunction and additional neuronal death. In addition, those components of oxidative stress must also be considered, including damaged mitochondria and immune mediated responses producing free radicals and reactive oxygen species (ROS) which add more damage to DNA, proteins, and cellular membranes. (Freire *et al.*, 2023)

The disruption of the blood-brain barrier, and explosive activation of inherent inflammatory pathways will increase the tissue damage. Importantly, a chronic neuroinflammatory environment is established when immune infiltrates occur with peripheral macrophages and microglia and release pro-inflammatory cytokines. This neuroinflammatory milieu not only worsens the acute tissue damage but also sets the stage for longer-term effects, including chronic neurodegenerative disease states, like Parkinson's and Alzheimer's diseases. Collectively, the pathological mechanisms cause diffuse axonal injury, brain edema, and neuronal cell death, all of which lead to the sustained cognitive and functional deficits seen in TBI patients. (Freire *et al.*, 2023)

Brain edema—an indicator of traumatic brain injury—is present within minutes post-impact, and occurs through cytotoxic and vasogenic mechanisms. Cytotoxic edema is caused by disruption of cerebral blood flow and blood-brain barrier (BBB) integrity, leading to hypoxia and loss of nutrients. The hypoxic environment compromises the sodium-potassium pump, and sodium

to accumulate intracellularly. The extracellular concentration of sodium creates an radient that ultimately causes astrocytes to draw water in through aquaporin water channels and swell. Vasogenic edema occurs through the plasma leakage of proteins and ions into the extracellular space due to compromised BBB integrity. Cytotoxic and vasogenic edema increase intracranial space leading to elevations in intracranial pressure, which compels the brain to maintain perfusion (i.e physiological flow of blood to brain) and can lead to herniation of brain tissue if uncompensated. (Zima *et al.*, 2024)

Neuroinflammation begins within hours after injury and can persist for months as a contributor to dual processes of recovery and degeneration. Both astrocytes and microglia facilitate neuroinflammation, and they can become reactive to injury. Astrocytes can become pro-inflammatory (A1 phenotype), producing neurotoxic proteins while losing non-neuronal protective functions, such as the regulation of glutamate, and enhance excitotoxicity; or the A2 phenotype with a milieu of beneficial repair. Microglia are the resident immune cells of the brain, and can become polarized into not only beneficial (M2, anti-inflammatory and phagocytic) or harmful (M1, pro-inflammatory) phenotypes. Beneficial M2 microglia help to clear away debris from neighboring cells but can lead to long-term inflammation and loss of synapses as harmful M1 microglia will take a longer response (a high-production of pro-inflammtory cytokines). (Zima *et al.*, 2024)

Mitochondria dysfunction is another core pathophysiological feature with both immediate and chronic electrical and metabolic consequences. After the spontaneous energy generation to restore ionic cell homeostasis (restoring brain cell ionic gradients), the brain enters a hypometabolic state for a prolonged stress response of diminished production of glucose metabolism and adenine-tri-phosphate molecules (ATP). Mitochondrial damage leads excessive production of reactive oxygen species (ROS) causing cell damage from the production of excessive reactive oxygen species (ROS) compromising mitochondrial DNA (mtDNA) and proteins leading to disrupted cellular respiration, abnormal apoptosis and necrosis. Mitochondrial membrane structural defects can release apoptotic factors in the cytosol during cell death, which can cause accidental death of cerebral cells leading to more neuronal loss. Mitochondrial cell biology is essential to the normal energetic recovery after TBI, and if normal mitophagy [(removal/delivery of damaged mitochondria through autophagy or other cellular processes)] is inhibited, there can be increased

stress and impaired cell recovery. Consequently, the coalescence of imagine capture of ons of cells under chronic injury, such impaired energy and cellular function often lead to failures of the cognitive and functional decline of brain function recovery after TBI. (Zima *et al.*, 2024)

2.4 Clinical features of TBI

Clinical indicators deemed adequate to support a diagnosis typically involve one or more of the following: acute intracranial injury on neuroimaging, neurologic impairments, unconsciousness, amnesia for peritraumatic events, and disorientation or similar evidence of disturbed mental status. Somatic symptoms (e.g., fatigue, nausea, headache, blurred vision, dizziness, hearing changes), cognitive symptoms (e.g., memory and executive function deficits), and emotional and behavioral issues (e.g., emotional lability, irritability, depression, and anxiety) are among the many symptoms that frequently follow TBI. (Howlett, Nelson and Stein, 2022)

2.5 Classification of TBI

The Glasgow Coma Scale (GCS) score, which was initially developed in 1974, is frequently used to evaluate a patient's state of consciousness after TBI. Excellent interobserver reliability has been demonstrated for the score, which gets better with training. Studies have demonstrated a linear association between the GCS score upon admission and the risk of death, and the postresuscitation GCS score has a significant effect on the outcome of TBI patients. (Swaminathan *et al.*, 2024)

Neurological status is often assessed by means of the Glasgow Coma Scale (GCS) which assesses eye, verbal, and motor responses to external stimuli. In Indonesia, both PERSPEBSI (Perhimpunan Spesialis Bedah Saraf Indonesia) and PERDOSSI (Perhimpunan Dokter Spesialis Saraf Indonesia) have issued guidelines that define TBI classification by GCS as standard clinical practice in Indonesia. According to the guidelines, TBI is classified into: (PERDOSSI, 2022)

TBI /Criteria	*GCS after 30 minutes of trauma*	*Structural Imaging*	*Loss of Consciousness Duration*	*Altered Mental Status Duration*	*Post-traumatic Amnesia*
Mild	13–15	Normal	< 30 minutes	≤ 24 hours	< 24 hours
Moderate	9–12	Normal / Abnormal	30 minutes – 24 hours	> 24 hours	1–7 days
Severe	3–8	Abnormal	> 24 hours	> 24 hours	> 7 days

2.6 Diagnosis of TBI

Over the last 20 years, research has demonstrated that GCS by itself may not be adequate for the diagnosis or prognosis of TBI, particularly in cases that are mild. Computed tomography (CT) is used in the current standard of treatment for TBI because of its quick acquisition time, specificity for bleeding, and ability to detect fractures. However, it has been demonstrated that magnetic resonance imaging (MRI) is becoming more significant for specific TBI subgroups. Because MRI can assess axonal shear, minor contusions, and hypoxic injury, it is more sensitive to almost all types of intracranial injury, with the exception of acute bleeding and fractures. MRI can assess volumetric loss in chronic TBI in addition to its application in acute TBI. (Yue *et al.*, 2020)

Patients with suspected TBI can be further diagnosed and/or risk-stratified using auxiliary diagnostic approaches such as blood biomarkers. In clinical settings, a number of blood biomarkers have been extensively investigated as possible indicators of TBI severity and risk classification. Tau protein, glial fibrillary acidic protein (GFAP), ubiquitin carboxy-terminal hydrolase-L1 (UCH-L1), neurofilament light protein (NF-L), S100 calcium-binding protein B (S100B), and others are among them. (Yue *et al.*, 2020)

One possible method for low-cost and minimally invasive TBI screening is the analysis of biomarkers present in circulating exosomes. Exosomes are membrane vesicles that range in size from 30 to 150 nm and are discharged into bodily fluids by living cells, including neurons. Cells in aberrant states, such as those that have experienced injury, apoptosis-related alterations, or

t transformation, show different protein and molecular signatures in their released . Blood-circulating exosomes have been investigated as possible targets for the emergence of cancer point-of-care diagnostic systems based on blood. However, exosomes can be damaged by existing exosome isolation technologies, which can lead to a loss of biomarkers and low yields. Additionally, affinity capture and conventional ultracentrifugation are slow (ranging from a few hours to several days), which restricts their application in point-of-care situations. (Wang *et al.*, 2021)

A study investigated whether the benefits of an acoustofluidic device could help with TBI early diagnosis using biomarkers in circulating exosomes. A well-characterized mouse model of closed-head injury was used to collect blood to mimic the neuropathology of TBI. Exosomes were separated from mouse plasma samples using acoustofluidics, and the amount of glial fibrillary acidic protein (GFAP) was measured. This allowed researchers to associate an exosomal biomarker for TBI with reactive astrocytes that responded to brain damage. Shortly after closed-head damage, the study found a rise in GFAP-positive exosomes. Exosomes derived from TBI mice exhibited higher intake rates than exosomes isolated from healthy controls, according to additional neuron intake experiments. These rates show that the isolated exosomes are bioactive and engaged in TBI pathology, proving that the acoustofluidic exosome separation technology is a potent technique for exosome-based TBI initial diagnosis and research. (Wang *et al.*, 2021)

Based on this meta-analysis, TBI subjects had substantially greater NfL levels than non-TBI subjects. In CSF, serum, and plasma samples, TBI was linked to a notably higher level of NfL expression than in non-TBI patients. Additional subgroup studies revealed that TBI significantly increased the level of NfL expression in the Caucasian population, but not in athletes. Furthermore, TBI significantly increased the NfL expression level only at 0–48 hours and 6–10 days sample collection time, suggesting that samples should be taken as soon as feasible following a TBI diagnosis. (Gao *et al.*, 2020)

2.7 Treatment of TBI

vasive Nonoperative Interventions

CP Monitoring: Invasive monitoring of intracranial pressure (ICP) is often necessary for patients who suffer moderate to severe TBI. Studies have shown that ICP monitors can reduce in-hospital and post-injury mortality, as stated in the 2016 Brain Trauma Foundation (BTF) guidelines. The recommendation is that medical practitioners should keep ICP values less than 22 mm Hg to prevent the development of secondary complications, as these higher ICP values correspond to higher mortality. (Abdelmalik, Draghic and Ling, 2019)

- *External* Ventricular Drainage (EVD): EVDs are catheters placed into the brain's ventricular system and are also known as ventriculostomies. EVDs are referred to as the most accurate and reliable measurement of ICP. It is even possible to reduce ICP through the removal of cerebrospinal fluid (CSF) which is important in managing severely increased ICP in TBI patients. For treatment of severe TBI, continuous drainage is available, and antimicrobial-impregnated EVDs are recommended to reduce risk of infection. (Abdelmalik, Draghic and Ling, 2019)
- *Alternative* ICP Monitoring Devices: Intraparenchymal monitors are a much less invasive option but cannot remove CSF or treat increased ICP immediately. While these monitors work about adequately for short-duration monitoring, accuracy becomes less reliable over time. There is a need for in depth, well planned care, especially with sedative and paralytic use but some studies do suggest that ICP control can reduce in-hospital mortality as well. (Abdelmalik, Draghic and Ling, 2019)

B) Non-invasive Nonoperative Interventions

- *Hyperosmolar Therapy:* Hyperosmolar agents like mannitol and hypertonic saline (HTS) have been commonly used to manage ICP in TBI patients, often with head elevation and controlled hyperventilation. Elevating the head by 30 degrees has shown reduction of ICP by increasing venous drainage and decreasing intracranial blood volume. Mannitol is a diuretic that can acutely decrease ICP, but it may have implications for patients experiencing hypovolemia. Clinicians will monitor serum osmolality around 320 mOsm/L as a suggested endpoint. (Abdelmalik, Draghic and Ling, 2019)

ypertonic saline has a similar effect on ICP without impacting blood volume (good for ood flow). HTS is often used in concentrations from 2-23.4% and is prepared with sodium chloride and sodium acetate to mitigate hyperchloremic acidosis. A reasonable target initially would be to achieve serum sodium from 145-155 mEq/L which correlates with osmolality of 300-320 mOsm/L. In emergency situations, higher concentrations of 23.4% HTS (30-60 mL bolus) have been used to reduce ICP, treat brain herniation, and preserve cerebral perfusion pressure (CPP). When ceasing HTS, a gradual taper has been suggested to mitigate rebound cerebral edema due to abrupt change in sodium concentrations. (Abdelmalik, Draghic and Ling, 2019)

- *Blood Pressure Control:* Managing blood pressure is important for TBI patients, as trauma can disrupt cerebral autoregulation. The BTF recommends systolic pressure of at least 100 mm Hg for patients ages 50-69, 110 mm Hg for other cohorts. This helps prevent inadequate CPP and allows for oxygenation of brain tissue. Norepinephrine or phenylephrine are preferred to raise blood pressures without affecting cerebrum vascular tone; but should be monitored closely as the higher CPP targets can cause respiratory distress. (Abdelmalik, Draghic and Ling, 2019)
- *Hypothermia and Anesthetics:* For patient with refractory ICP, sedatives like pentobarbital and propofol combined with hypothermia can decrease metabolic demands of the brain, decreasing ICP and improving oxygenation. The BTF recommends high-dose barbiturate therapy for persistently elevated ICP. Propofol has also been effective; both agents should not be routinely administered to prevent intracranial hypertension without elevated ICP. (Abdelmalik, Draghic and Ling, 2019)

C) Surgical Interventions

Hemicraniectomy: Under certain circumstances when brain swelling is significant and pressing against the skull, hemicraniectomy (the surgery that involves removal of part of the skull) can be an important element of treatment to relieve pressure to mitigate further brain injury. According to the BTF guidelines of practice, if hemicraniectomy is performed, a significant frontotemporoparietal piece, preferably at least 12 x 15 cm is suggested, while both frontal bones should generally not be removed. Although hemicraniectomy can be performed in an emergency

nce, an early cranioplasty following hemicraniectomy appears to be associated with recoveries and better long-term outcomes; this allows to proactively address urgent cases effectively. (Abdelmalik, Draghic and Ling, 2019)

2.8 Mannitol

Mannitol is a sugar alcohol that is water soluble that has the chemical formula C6H8(OH)6, and it is primarily used as an osmotic diuretic. The pH of mannitol is 6.3, which is naturally acidic, and mannitol can also be compounded with sodium bicarbonate in pharmacy preparations in order to help neutralize the pH for safer use in treatment. (Kim *et al.*, 2023)

A) Pharmacokinetics

- *Absorption:* Mannitol, which is given IV, has limited absorption in the GI tract. Mannitol has a rapid onset, which allows it to serve a crucial role in emergency medicine, when the goal is to perform medication which is decreasing intracranial pressure (ICP). If given IV, mannitol will lower ICP in approximately 15–30 minutes, with a duration of action 1.5-6 hours. The desired clinical endpoint for mannitol is diuresis, or increased urine production, which occurs after mannitol administration in the time frame of 0.5-3 hours. (Kim *et al.*, 2023)
- *Distribution:* Mannitol mostly remains present in the extracellular fluid of the body and, by virtue of its minimal permeability across the blood-brain barrier (BBB), does not appreciably penetrate the brain tissue. Its negligible delivery to brain tissue is demonstrated by an osmotic reflection coefficient of 0.9 (a value closer to one suggests that penetration of the BBB is mostly impeded).

  When mannitol is utilized to treat brain edema for an extended period of time, there is a chance that small amounts of mannitol will sporadically cross the BBB and equilibrate in brain tissue. This gradual shift in osmotic balance may eventually cause a rebound effect, where liquid is drawn into the brain; stopping mannitol too quickly can lead to worsening cerebral edema. Because of this, once a patient has been treated with mannitol for a

olonged period of time a taper regimen or step down with a different osmotic agent is pically recommended to allow the brain to readjust and avoid this complication. From a renal perspective, mannitol is freely filtered across the glomeruli and is neither reabsorbed or secreted by the kidney, which is the basis for its predictable clearance through urine. All of this demonstrates why mannitol is a reliable osmotic diuretic; however, it still needs to be monitored in the context of a long-term administration.

- *Metabolism:* Although mannitol is primarily eliminated unchanged in the kidneys, a small amount is metabolized in the liver. The metabolism of mannitol is accomplished mainly by the enzyme mannitol dehydrogenase that oxidizes mannitol to fructose, which can then be utilized in the body within the energy cycle. Fructose is phosphorylated to fructose-1-phosphate when fructose and ATP are joined by fructokinase. After phosphorlation, fructose-1-P is cleaved by aldolase B into two main substrates, dihydroxyacetone phosphate (DHAP) and glyceraldehyde.

  These substrates are glycolytic metabolites and eventually DHAP and glyceraldehyde become substrates for energy (ATP) production. Although this pathway represents a minor path for mannitol used in clinical practice, this does demonstrate the potential of mannitol as a contributor to the cellular energy flux through metabolic pathways that my be interesting for consideration regarding the demands of surgery on cerebral metabolism. (Kim *et al.*, 2023)

- Excretion: Mannitol is excreted unchanged mainly by the kidney and the rate of renal clearance is almost equal to the rate of glomerular filtration rate (GFR). Mannitol has an elimination half-life of 0.5-2.5 hours in individuals with intact renal function, and possibly extended to 6 to 48 hours in those with impaired renal function. (Kim *et al.*, 2023)

B) Pharmacodynamics

Following the administration of mannitol, the increased concentration of mannitol in the blood leads to an increase in blood osmotic pressure. The osmotic shift caused by mannitol draws water from the surrounding tissues into circulation, and plasma volume has been temporarily expanded. This mechanism does help in reducing cerebral or ocular pressure through shift of fluid from

ıpartments, but this increase in plasma volume must also be closely monitored--
in patients with heart failure--due to the risk of pulmonary edema from sudden increase in plasma volume.

Mannitol is a low molecular weight compound (182.17 g/mole), is filtered freely by the glomerulus and is not reabsorbed by the renal tubules. The presence of mannitol in the nephron raises osmotic pressure in the tubular flow, which leads to osmotic diuresis. Approximately 80% of the administered mannitol is excreted unchanged in urine, and it encourages water loss. In the setting of acute oliguria, mannitol has the potential to stimulate diuresis and provide some protection against acute kidney injury, even when the glomerular filtration rate (GFR) is reduced due to poor volume status.

The effect of mannitol on sodium levels are dependent on time and dose. In acute acute situations, the increased urine flow will lead to increased sodium excretion then the increased flow of fluid from other compartments may lead to dilutional hyponatremia. However, with chronic use, the volume of water lost from the body may exceed the amount of sodium lost, which will lead to hypernatremia. High doses of mannitol given in the setting of renal failure, and heighten the odds of mannitol accumulating in the body. This will raise osmotic pressure and cause considerable fluid shifts into the vascular compartment, and the development of dilutional hyponetremia or further A Bayesian effect on fluid imbalance.

C) Mannitol for TBI

Mannitol is a sugar alcohol that is present in fruits and vegetables. Mannitol is an osmotic diuretic that is used to reduce increased intracranial pressure (ICP) in patients when increased ICP is due to traumatic brain injury (TBI). Mannitol's primary mechanism is to create a strong osmotic gradient via the blood-brain barrier (BBB). Mannitol does not cross an intact blood-brain barrier and therefore can draw out excess water from the brain tissue into circulation and thereby help decrease the cerebral edema and raise ICP. (Poudel et al., 2023; Abdulhamid et al., 2022; Kim et al., 2023; Nagavalli and Nanthagopal, 2023)

Mannitol, in addition to the osmotic effect, improves cerebral blood circulation perfusion by decreasing blood viscosity through mechanisms that help decrease hematocrit and improve red

. deformability, together reducing the microcirculatory resistance to blood flow and g blood perfusion to brain tissue (Poudel et al., 2023; Kim et al., 2023). Mannitol can also cause some mild cerebral vasoconstriction and therefore can decrease the cerebral blood volume, which further helps to control ICP (Kim *et al.*, 2023). Once mannitol is in circulation, it is freely filtered from renal circulation and not reabsorbed. Mannitol will increase osmolarity in the renal tubules and induce diuresis. Mannitol not only induces diuresis to help excrete excess solvent, but it helps to excrete sodium, chloride and other solutes in the urine(Nagavalli and Nanthagopal, 2023). Thus, mannitol serves a dual function of decreasing ICP and promoting fluid-electrolyte balance and diuresis.

However, like all therapies, must be used judiciously, not as a long-term therapy or for excessive exposures. If mannitol starts to accumulate particularly in patients with impaired renal function, the osmotic gradient becomes even larger, and will lead to a rebound and increase ICP, not to mention, kidney toxicity and hypovolemia from excessive diuretic effects .

To summarize, the ability of mannitol to dehydrate the brain, improve cerebral hemodynamics and promote renal clearance explains its continued use in the acute neurocritical-care setting. Mannitol acts as an osmotherapy at several different targets and is a safe and effective, albeit not complication free, therapy for the management of TBI. (Poudel et al., 2023; Abdulhamid et al., 2022; Kim et al., 2023; Nagavalli and Nanthagopal, 2023)

2.9 Dexamethasone

Dexamethasone (MK-125) is a synthetic fluorinated corticosteroid at position 9 that is widely used for the treatment of multiple disorders including inflammatory, allergic, respiratory, and autoimmune diseases and some tumors. (PubChem, 2024))

A) Pharmacokinetics

Dexamethasone's pharmacokinetics are dose-proportional for oral administration within the range of 0.5 to 40 mg. Tmax occurs at about an hour following a single oral dose of dexamethasone but with a wide range from 0.5 to 4 hours. If taken with significant high-fat, high-calorie food, peak

tion can decrease by 23%. Approximately 77% of dexamethasone is bound to plasma n the blood. The mean terminal half-life of dexamethasone is approximately 4 hours and its oral clearance rate is 15.7 L/hr. Dexamethasone is primarily metabolized by CYP3A4 and less than 10% of the dexamethasone that is ingested can be excreted in urine which suggests limited renal elimination. (Johnson and Kelley, 2022)

B) Pharmacodynamics

Dexamethasone possesses strong glucocorticoid properties with little to no mineralocorticoid properties, it produces a complete array of actions in the body. Dexamethasone operates by limiting the movement of neutrophils and limiting the growth of lymphocyte colonies that control the inflammatory response. This process reduces capillary membrane permeability and stabilizes lysosomal membranes. Dexamethasone also affects serum levels of vitamin A, inhibits specific immune responders such as prostaglandins, interleukin-1, interleukin-12, interleukin-18, TNF, interferon-gamma, and granulocyte-macrophage colony-stimulating factor. Dexamethasone is also noted to improve lung function possibly through increased surfactant production, and improved pulmonary circulation. In the body, dexamethasone is metabolized by the liver and is excreted in the urine. (Johnson and Kelley, 2022)

C) Dexamethasone for TBI

Dexamethasone (DX) is a glucocorticoid primarily used to manage CNS injuries and related issues due to its powerful anti-inflammatory actions, particularly in conditions like brain tumors, severe brain diseases, stroke, and even recent COVID-19 treatments. Although dex allows for anti-inflammatory treatment of these conditions, it has a major limitation related to the treatment of brain conditions: it is actively removed by P-glycoprotein, which limits brain accumulation of dex. This limits its effect anti-inflammatory treatment of brain inflammation. Additionally, dex can cause a number of side effects with long-term treatment such as issues with glucose metabolism, impaired immune function, and even neuropsychiatric symptoms, which range from mood changes to more developed psychological symptoms. Thus, while dex can effectively cause reduced inflammation, study on the long-term outcome of patients with traumatic brain injury (TBI) show that the treatment has little advantage over placebo in terms of long-term therapy, potentially

even lesser therapeutic advantage for TBI cases, particularly over longer use periods *al.*, 2024)

Dexamethasone (DX) greatly reduces early pro-inflammatory cytokines when used at very high doses (high doses method of treatment for head trauma for the last 40 years) but high dose treatment carry a certain risk of unwanted effects such as diabetes, glaucoma, and potentially osteoporosis. The CRASH international randomized double-blind trial demonstrated a relative increase in death, with patients with moderate to severe TBI treated with high-dose synthetic glucocorticoids (GCs) such as DX. While there have been numerous other studies, there has been no significant therapeutic benefit to the use of GCs at high doses, and as such the majority of recent clinical guidelines and summaries generally do not recommend dex administration at higher doses for TBI. The recent publication of low-dose dex provides evidence for a potential therapeutic mechanism through thorough reduction of secondary injuries, and potentially, support functional recovery. (Macks *et al.*, 2022)

Sustained delivery of dexamethasone with a PEG hydrogel (polyethylene glycol-bis-acryloyloxy acetate) physically bound to hyaluronic acid (PEG-bis-AA/HA-DXM) is an effective method to attenuate secondary injury when administered after moderate TBI. Delivery through PEG-bis-AA/HA-DXM emphasizes the localized release of dexamethasone to the injury over the long term while lowering the risk of the side effects common with high systemic doses of glucocorticoids. The hydrogel treatment improved overall motor coordination as measured with the beam walk and rotarod during the first week post-injury. More importantly, the behavioral performance in the tests described above was associated with histological results showing reduced lesion volume, decreased markers of neuroinflammation, astrogliosis, and apoptosis in the injury hemisphere. Furthermore, compared to untreated TBI controls, rats which received PEG-bis-AA/HA-DXM had greater neuron counts in the perilesional cortex. GFAP expression is a sign of low astrocyte activation which may have resulted in less glial scar formation and allowed for a more plastic form tissue repair in the injured tissue. Most important, this low-dose dexamethasone hydrogel treatment resulted in therapeutic benefits that could not be achieved at the level of systemic dexamethasone high-dose regimens; these benefits include strain reductions in apoptotic cells and increasing markers of neuronal protection, all with reduced levels of systemic side effects. (Jones *et al.*, 2023)