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Correlation of Bleeding Volume and Cognitive Function Impairment in Hemorrhage Traumatic Brain Injury

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ABSTRACT

Background/aim: Traumatic Brain Injury (TBI) is a neurological emergency. When a traumatic brain injury occurs, there will be short-term and long-term effects that will affect the brain. This study was aimed to determine the correlation of bleeding volume and cognitive function impairment in hemorrhagic traumatic brain injury.

Method: This study uses data collection methods in the form of interviews with samples which will later be presented in the form of analytical observational study. Consecutive data collection on TBI patients in poly and unit room medical neurosurgery at Sanglah Hospital from August – Oktober 2021. The questionnaire used to cognitive function impairment withMontreal Cognitive Assessment version Indonesia (MoCA-INA). Data analysis using SPSSVersion 23 for windows.

Results: A total of 42 subjects were divided into normal and decreased cognitive function The patients' mean age was average 29 (17-49) years old, Man 62%, cases epiduralhemorrhagic 50 %, subdural 38% and intracerebral 12%, and their mean Glasgow Coma Scale score at admission was 11.5 ± 1.7 and significant with OR = 0.1 (95% CI = (0.02-0.4;p = 0.003) were. Lesions were predominantly localized to the frontal (14 lesions) and temporal (10 lesions) lobes. Lobe lesion volume did not correlate with cognitive function.The volume bleeding average 10.43 (1-40) significant with p= 0.016 (OR 5.2 (95% CI (1.3-19.7).

Conclusion: Bleeding volume in hemorrhagic TBI increased five times in volume > 10 mL and GCS 9-13 first times came emergency room significant increased 0.1 times decreased function cognitive.

Keywords: sleep quality, non-vegetarian, diet, serotonin, vegetarian

INTRODUCTION

Traumatic Brain Injury (TBI) is a neurological emergency that has complex consequences, because the head is the center of a person's life. Inside the head there is a brainthat affects all human activities, if there is damage it will disrupt all body systems.[1] Brain Injury Association of America states that TBI is a damage to the head that is not congenital or degenerative but is caused by an attack or physical impact from the outside that can change consciousness, causing damage to cognitive abilities and physical function. TBIis a disturbance in the normal functioning of the brain that can caused by an outside force, such as a blow to the head or penetrating injury. Due to TBI there will be changes in brain function that can cause decreased consciousness, memory loss for previous events (retrograde) or after injury and focal neurological deficits in the form of weakness, loss of balance, vision changes, dyspraxia, loss of sensory function and aphasia. Changes in mentalstate at the time of injury may include confusion, disorientation and decreased thinking.[2]

Traumatic brain injury can cause a significant increase in mortality rates in patients dueto trauma and occurs in 2% of the population each year so that it is still the leading cause

of death and disability in young adults. Nearly 75% of fatal accident victims show evidence of a head injury at post mortem examination. In the United States the incidence of head injuriesis estimated at 200 per 100,000 people and about 80% are minor head injuries, 10% are moderate head injuries and 10% are severe head injuries. Head injuries often occur in men aged between 15 - 24 years and the incidence of head injuries in men (55.4%) is higher than women due to high mobility among productive age.[3]

According to Riskesdas in 2018, the prevalence of head injuries in Indonesia was 11.9%. Head injuries occupy the third position after injuries to the limbs. In the province of Bali, it was found to have a prevalence of 10.7%.[4] Another study showed an increase in cases of head injuries in the world and 1.3 million people of whom came to the hospital. Until now, data on head injury is very difficult to compare with multinationals because of many things such as inconsistent data, very complex diagnosis, different injury case definitions and unequal diagnostic criteria. A retrospective study by Pradip et al., found that in developed countries there were about 17% of TBI patients requiring surgery and classified as 84% mild injury, 9% moderate injury and 7% severe injury. Two-thirds of TBI complications in the form of permanent disability and cannot return to its pre-injury condition. That TBI can occur in all age groups, the incidence in males is higher than in females and the highest incidence is in young adults (aged 15-24 years).[5]

The majority of survivors of TBI recover fully from the injury, or at least recover sufficiently to continue to function independently throughout most of their adult life.However, little is known of the impact of TBI on outcomes decades later when the effects ofthe injury interact with the aging brain. Given the protracted time between many TBIs and onset of dementia and the difficulty in randomizing TBI patients in clinical trials, the proposed link between TBI and dementia has been primarily based on findings fromretrospective epidemiologic studies. Numerous case-control studies have reported an association between a history of closed head injury and Alzheimer's disease (AD) or dementia more generally.[6] This may have influenced the accuracy of the report of exposure to head injury. A third community cohort study of subjects enrolled when they were 65 yearsand older had 14% of the participants report a history of head injury at baseline; after an average of 7.4 years of follow-up, they found no association between self-reported TBI at baseline and incident dementia.[6] The researchers wanted to examine whether there is a relationship between bleeding volume and cognitive function impairment in hemorrhagic traumatic brain injury.

METHODS AND PROCEDURES

This study uses data collection methods in the form of interviews with samples which will later be presented in the form of analytical observational study. Consecutive data collection on TBI patients in poly and unit room medical neurosurgery at Sanglah Hospital from August – Oktober 2021. The ethical permission in this study with No. 2349/UN 14.2.2VII.14/LT/2021 from the research ethics commission of the Faculty of Medicine, Udayana University/ Sanglah Central General Hospital Denpasar. The questionnaire used to cognitive function impairment with Montreal Cognitive Assessment version Indonesia (MoCA-INA). Score cut off less than 26 indicates cognitive impairment. For the level of formal education 4-9 years, 2 points are added to the total score, while for the formal education level 10-12 years, 1 point is added.[7]

Inclusion criteria in this study: 1) Mild-moderate traumatic brain injury, GCS 14-15 and GCS 9-13, with a CT scan of the head without contrast bleeding, 2) Onset of brain injury
< 24 hours, 3) 17-50 years old, 4) Patients can use language and written in Indonesian, 5) Patients are willing to participate in the study after receiving an explanation of the

aims, objectives and complete research procedures by signing a informed consent, 6) During the examination, the patient must have good attention.

The exclusion criteria are as follows: 1) Patients with a history of other neurological diseases: stroke, seizures, and intracranial infections, 2) Presence of multiple traumas, 3) Presence of impaired cognitive function pre-traumatic brain injury, i.e. if the value of Short Form of the Informant Questionnaire on Cognitive Decline in the Elderly (Short IQCODE)
4) There is a decrease in consciousness or a change in the quality of consciousness 5) Having depression. Data analysis using SPSS Version 23 for windows.

RESULTS

The study involved 42 patient hemorrhagic traumatic brain injury subjects who met the eligibility criteria, grouped into groups with normal (21 subjects) and decreased (21 subjects) cognitive function with MOCA-INA Questionnaire test. The characteristics of respondent assessed in this study included gender, age, marital status, level of education, job status, andbleeding volume at **table 1**. The correlation of bleeding volume and cognitive function at **table 2**

Table 1 Characteristics of Subjects

Variable		Normal Cognitive Function n(%)	Decreased Cognitive Function n(%)
Age (years) mean (min-max)		29.3 (17-49)	29.8 (17-48)
Age (years)	≤ 30	17 (40.5)	13 (31)
	> 30	4 (9.5)	8 (19)
Gender	Man	16 (38,1)	16 (38,1)
	Female	5 (12)	5 (12)
Marital status	Married	12 (28.6)	14 (33.3)
	Not married	9 (21.4)	7 (16.7)
Level of education	Senior High School	9 (21.4)	13 (31)
	Academy/ collage	12 (28.6)	8 (19)
Job Status	Government Employers	4 (9.5)	3 (7.1)
	Private employer	7 (16.7)	5 (11.9)
	Entrepreneur	7 (16.7)	4 (9.5)
	Does not work	3 (7.1)	9 (21.4)
Bleeding volume	> 10 mL	16 (38,1)	8 (19)
	≤ 10 mL	5 (12)	13 (31)
Type of hemorrhagic traumatic brain injury	Subdural	8 (19)	8 (19)
	Epidural	11 (26.2)	10 (23.8)
	Intracerebral	2 (4.8)	3 (7.1)
Mechanism of injury	Ped vs MV	3 (7.1)	4 (9.5)
	MVA	7 (16.7)	20 (47.6)
	Motorcycle vs MV	3 (7.1)	4 (9.5)
	Motorcycle	4 (9.5)	2 (4.8)
	Bicycle	1 (2.4)	1 (2.4)
	Fell down stairs	1 (2.4)	2 (4.8)
Hemorrhage Location	Frontal	8 (19)	6 (14.3)
	Frontal, temporal	2 (4.8)	2 (4.8)
	Temporal, basal ganglia, splenium	2 (4.8)	3 (7.1)
	Parietal	1 (2.4)	0
	Temporal	5 (12)	5 (12)
	Basal ganglia	1 (2.4)	4 (9.5)
	Frontal, temporal, occipital	2 (4.8)	0
GCS	9-13	8 (19)	18 (42.9)
	14-15	13 (31)	3 (7.1)
GCS mean (min-max)		13.5 (9-15)	11.5 (9-15)
Bleeding volume mean (min-max)		5.7 (1-25)	10.43 (1-40)
MOCA-INA mean (min-max)		28.8 (27-30)	22.9 (18-26)

GCS= glasgow coma scale; MOCA-INA: The Montreal Cognitive Assessment-Indonesian Version MV = motor vehicle; MVA = motor vehicle accident; ped = pedestrian; splenium = spleniumof the corpus callosum

Based on the bivariate analysis using the Chi-square test, there was a significant correlation of bleeding volume and cognitive function in traumatic brain injury patients with OR = 5.2 (95% CI = (13-19.7; p = 0.016). The bleeding volume > 10 mL in traumatic brain injury patients have an increased risk of experiencing a decreased cognitive function four times compared to the bleeding volume < 10 mL.

Other factors that also affect the risk of decreased cognitive function in the traumatic brain injury including gender, age, marital status, level of education, mechanism of injury, hemorrhage location, GCS, and job status which will be analyzed bivariate with the results obtained in **table 3.**

Table 3 Bivariate analysis of other variables on risk factors cognitive function impairment

Variable		**Normal cognitive function n (%)**	**Decreased cognitive function n (%)**	**OR IK 95%**	**P***
Gender	Man	16 (38,1)	16 (38,1)	1 (0.2-4.1)	1.000
	Female	5 (12)	5 (12)		
Age	≤ 30	17 (40.5)	13 (31)	2.6 (0.6-10.6)	0.715
	> 30	4 (9.5)	8 (19)		
Marital status	Married	12 (28.6)	14 (33.3)	0.6 (0.1-2.3)	0.526
	Not married	9 (21.4)	7 (16.7)		
Level of education	Senior High School	9 (21.4)	3 (31)	0.4 (0.1-1.5)	0.219
	Academy/ collage	12 (28.6)	8 (19)		
Job Status	Work	3 (7.1)	7 (16.7)	0.3 (0.7-1.5)	0.777
	Not working	18 (42.9)	14 (33.3)		
Mechanism ofinjury	Sigle accident	15 (35.7)	13 (31)	1.5 (0.4-5.6)	0.514
	Accidents with opponents	6 (14.3)	8 (19)		
Hemorrhage Location	One region	13 (31)	12 (28.6)	0.8 (0.2-2.9)	0.739
	> 1 region	8 (19)	9 (21.4)		
GCS	9-13	8 (19)	18 (42.9)	0.1 (0.02-0.4)	0.003 †
	14-15	13 (31)	3 (7.1)		

Based on the bivariate analysis using the Chi-square test, there was a significant correlation of other factors that also affect the risk of decreased cognitive function significant of GCS first time come to emergency with OR = 0.1 (95% CI = (0.02-0.4; p = 0.003). The GCS 9-13 first time come to emergency in traumatic brain injury patients have an increased risk of experiencing a decreased cognitive function 0.1 times compared GCS 14-15.

DISCUSSION

This study knows incidence in men (76%) was more than female (24%), on data from National Center for Injury Prevention and Control, Centers for Disease Control and Prevention (CDC), in the United States approximately 1.7 million people experience traumatic brain injury and is the third most common cause (30.5%) of trauma-related deaths in America. With 52,000 cases of whom died, 275,000 cases were hospitalized, man more than female.[3] In the UK, COT was the primary diagnosis in 77,239 patients presenting to hospital in the period 2013-2014.[8]

In Indonesia, the proportion of traumatic brain injuries based on the results of Indonesian Health Service 2018 shows the incidence of traumatic brain injury is 4 per 10 population, and in Bali with a higher incidence rate of 6 per 10 population. The incidence ofhead injury mainly occurs in the productive age group between 15-44 years.[9] This study majority age ≤ 30 years more than > 30 years for cases activity to traffic accidents. TBI canresult from trauma ranging from a simple blow to the head to a penetrating injury to the brain.In the United States, around 1.7 million people suffer a traumatic brain injury, with adolescents between ages 15 and 19 and adults age 65 and older among the most likely to sustain a traumatic brain injury. Mild traumatic brain injury (mTBI), also known as a brain concussion, initially was considered to be a benign occurrence.[1] This same with this

study were mild injury with GCS 9-13 26 respondent (62%) more than GCS 14-15 and significantfor analysis with OR = 0.1 (95% CI = (0.02-0.4; p = 0.003).

In Sanglah Hospital, the most common causes of death due to accidents are multiple trauma (16%), head trauma (4%), abdominal trauma (1%) and thoracic trauma (1%).[10] Based on research conducted at Hasan Sadikin Hospital from 2008-2018, TBI was found to be 3578 cases, the incidence in men (79.8%) was higher than women (20.2%), with the highest age group 18-45 years.[11] Age in the study with average 29 years old with min-max(17-49).

When a traumatic brain injury occurs, there will be short-term and long-term effects that will affect the brain. The initial process causes primary injury as a result of mechanical damage, stretching, tearing, and/or pulling of neurons, axons, glia, and blood vessels.Primary injury can be diffuse, focal, or a combination of both, so the damage will be heterogene.[12]

Primary injury will initiate the activation of secondary injury which includes systemic complications and cellular injury that occurs within hours to weeks after the primary injury. Systemic disorders include edema, increased intracranial pressure (ICP) all of which will contribute to decreased cerebral blood flow and impaired metabolism leading to ischemia. This ischemia will contribute to the initiation of biochemical and cellular cascades including: glutamate excitoxicity, calcium overload, free radical formation, mitochondrial dysfunction, inflammation, and activation of pro-apoptotic genes. This cellular injury results in neuronal cell loss through necrosis (rapid, uncontrolled), and programmed (delayed) cell death. It was originally thought that most axonal injuries occur due to tearing and cutting of axons during the primary injury. It is currently known that axonal degeneration is the result of secondary biochemical activation and cellular injury.[13]

In addition to neuronal cell loss and axonal degeneration, impaired synaptic plasticity also contributes to cognitive dysfunction in mild to moderate TBI cases where no cell loss is detectable. TBI will induce abnormalities in neurotransmitter systems (such as: cholinergic, monoaminergic, and catecholamines) which have a role in cognitive.[5] Disruption of homeostasis after TBI will affect signaling pathways including protein kinase CaMKII and MAPK which have an important role in the induction of long-term potentiation/long-term potentiation (LTP) and long-term depression/ long-term depression (LTD) which are the two main mechanisms underlying learning and memory.[14]

Elevated extracellular glutamate levels are the initial event responsible for calcium overload and secondary damage after TBI. The increase in extracellular glutamate comes from several sources. Mechanical damage from primary injury will damage cell membranesthereby releasing glutamate into the extracellular space. Membrane depolarization due to ionimbalance-induced injury can increase glutamate vesicle release. In addition, injury-inducedenergy depletion also causes failure of extracellular glutamate uptake by ATP-dependent glial glutamate transporters. The effect of the whole process causes a large increase in extracellular glutamate levels after TBI.[15]

Excitotoxicity causes neuronal injury through two phases. The first phase is characterized by sodium-dependent neuronal swelling due to activation of ionotropic glutamatrgic receptors resulting in sodium channel opening, Na+ (and Ca++) ion influx, K+ efflux followed by calcium-dependent neuronal degeneration. The influx of Na+ ions cause membrane depolarization, opens calcium channels and removes magnesium block at the NMDA receptor causing more calcium to enter the cytosol. Calcium influx is further amplified by changes in the composition of AMPA receptor subunits (loss of GluR2subunits), making it easier for calcium to pass. In addition to acting on ionotropic receptors, glutamate can also activate group 1 metabotropic glutamate receptors thereby stimulating the opening ofvoltage-gated calcium channels and

increase calcium influx. The effect of calcium influx with energy failure will initiate the release of intracellular storage of calcium ions.[12] High levels of intracellular calcium trigger activation of secondary biochemical cascades that result in the initiation of programmed cell death and loss of neurons and synapses in vulnerable brain areas such as the hippocampus and result in cognitive dysfunction. Increased intracellular calcium initiates several cellular pathways such as phospholipase activation calcineurin (CaN), proteases that include calpains (calcium dependent proteases) and caspases (calcium dependent phosphatases), transcription factors including c-Fos, c-Jun, and c-myc, nitric oxide synthase (NOS), as well as DNA Degrading Endonucleases. As a result, the DNA will be fragmented, the structure and cell membrane will be damaged. This will result in cell death through apoptosis and necrosis. Activation or overproduction of these molecules can lead to degradation of cytoskeletal components (loss of dendritic spine), mitochondrial dysfunction, oxidative stress, and activation of pro-apoptotic genes.[1]

Another secondary cell death event that occurs after traumatic brain injury is oxidative stress, characterized by an overaccumulation of Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS). Due to their highly reactive nature, free radical levels arenormally kept low through regulation of production and rate of degradation by enzymes and antioxidants. After TBI, there will be a significant increase in ROS and a decrease in anti- oxidant levels. When the formation of ROS and RNS is too large, it will cause major cell dysfunction and its oxidative ability will damage all biomolecules. ROS cause lipoperoxidation of cell membranes, which causes dysfunction of several structures and organelles, such as mitochondria and oxidizing proteins that affect membrane pore. ROS can also break down DNA and cause mutations. ROS are also associated with neutrophil infiltration, which induces an inflammatory response which in turn increases ROS formation. Overall, the oxidative stress cascade causes massive neuronal cell death.[16]

Mitochondrial dysfunction is also thought to be a key secondary mechanism of cell death in traumatic brain injury. Mitochondria are the main source of ROS in the electron transport chain. After head trauma, the mechanism for stabilizing ROS levels is disrupted and increased. Lipid peroxidase-mediated oxidative damage to the mitochondrial membrane will negatively affect its structure and function. Mitochondria also act as calcium ion buffers, releasing and absorbing as many ions as needed to maintain homeostasis. But when there are too many calcium ions for excitotoxicity, mitochondrial function will be disturbed. Mitochondrial permeability transition pore associated with the inner mitochondrial membrane is calcium dependent. With excess calcium ions, the pores will remain active, damage the mitochondrial membrane potential. Without a membrane potential, mitochondria cannot produce ATP, and ATP synthase will instead consume ATP instead of producing it. Due to mitochondrial breakdown, toxins and apoptotic factors are released into cells, activating caspase-dependent apoptosis. This causes cells to die. [16]

Primary injury will damage tight junction, causes an influx of peripheral immune cells and circulating factors (albumin, thrombin, and fibrinogen). This event will affect the interaction between blood-brain barrier endothelial cells and astrocyte glial cells and will later contribute to blood-brain barrier dysfunction by increasing its permeability (secondary injury). The blood-brain barrier consists of tightly connected endothelial cells, but their normal function depends also on the surrounding glia and astrocytes. The blood-brain barrier is highly selective, providing an environment for brain parenchyma cells free of these factors blood-borne and immune cells. One of the mechanisms of blood-brain barrier dysfunction after traumatic brain injury isup-

regulation from matrix metallopeptidase protein (MMP-9), which will destroy tight junctions. The breakdown of the blood brain barrier also causes an influx of larger molecules such as leukocytes which increases the osmotic pressure in the brain. This will lead to edema and increased intracranial pressure, which is directly related to ischemia and cell death. Another impact of the damage to the blood brain barrier is cognitive decline and the limited effectiveness of therapy.[17,18]

TBI-induced neuroinflammation is a complex process with neuroprotective and neurotoxic components. Following injury, an endogenous inflammatory response is triggered to protect the site of injury from invading pathogens and repair damaged cells. Complementis activated to perform its function and recruit inflammatory cells in the intrathecal compartment. Complement activation is also followed by the infiltration of neutrophils, monocytes, and lymphocytes that cross the blood-brain barrier, then secrete prostaglandins, free radicals, proinflammatory cytokines, and other inflammatory mediators which will then increase the expression of chemokines and cell adhesion molecules. Resident astrocytes and microglia in the CNS are activated in response to damage to the blood-brain barrier. Resident and peripheral microglia cells that are systemic macrophages have a protective response against traumatic brain injury, limiting damage by separating injured tissue from healthy tissue. Activated glia will secrete a number of proinflammatory cytokines and neurotoxic chemokines. Levels of proinflammatory cytokines such as Tumor necrotic factor (TNF), Interleukin 1ß (IL-1ß) and Interleukin-6(IL-6) increases dramatically in the hours after TBI. Attachment to cytokine receptors activates a number of intracellular signaling pathways including c-Jun Terminal kinase (JNK), p38 mitogen activated protein kinase (p38/MAPK) and extracellular signaling-related kinase (ERK) which has a role in synaptic plasticity. Cytokine attachment can trigger cell death through activation of caspases. Up-regulation of these cytokines will increase the permeability of the blood-brain barrier by overexpression of cell adhesion molecules on endothelial cells and through increased production of chemokines and sustained microglial activation. In addition to secreting cytokines, microglia also secrete several substances including ROS and nitrogen species such as glutamate, which normally play an important role in neural transmission but when microglia are chronically activated under inflammatory conditions contribute to neuronal cell death. Neuroinflammation and chronic microglial activation have been shown to play an important role in post-TBI cognitive dysfunction.[18,19]

TBI will significantly interfere with cAMP signaling and cause a decrease in hippocampal synaptic plasticity. In previous studies, it was found that the decrease in cAMP was associated with upregulation of the enzyme that degrades cAMP, namely phosphodiesterase 4(PDE4). There are 4 subfamilies of PDE4, which are encoded by different genes (AD). Research in mice shows the PDE4 genes have different functions in the brain. PDE4A is involved in anxiety, PDE4B regulates inflammation and alters anxiety levels, PDE4C is not a major isoform in the brain or immune system, and PDE4C is involved in memory formation, depression, and neurogenesis.[19]

This study result for significant correlation of bleeding volume and cognitive functionin traumatic brain injury patients with OR = 5.2 (95% CI = (13-19.7; p = 0.016).. The bleeding volume > 10 mL in traumatic brain injury patients have an increased risk of experiencing a decreased cognitive function four times compared to the bleeding volume <10 mL. this same with twelve percent of the cohort self reported a history of head injury, but typical of community samples, reported head injuries tended to be relatively mild. In addition, the average time between the collection of TBI history and the diagnosis of AD was 2.1 years, raising the question of whether some of those with AD were already in the early stages of the disease when the

TBI history was collected.[20] The clinical impact of TBI is not only its high mortality rate (contributing to one third of injury-related deaths in America), but also its long-term complications. To date, it is estimated that approximately 3.2-5.3 million people with TBI in the United States have TBI and as many as 8 out of 10 cases report cognitive impairment. The high prevalence of cognitive impairment is due to hippocampal susceptibility, which shows bilateral atrophy several years after injury even when no direct injury has occurred.[18,21]

Mild TBI characterized by impaired short-term memory and attention occurs in 75-85% of patients with TBI in both the general population and the military population. That same with this study were mild TBI 62% in all case. It is increasingly becoming apparent that recurrent mild TBI in at-risk populations such as athletes and military personnel can cause significant long-term emotional and cognitive impairment.[6] The consequences of TBI can be short-term and long-term cognitive deficits. Deficits usually occur in attention, learning, memory, and higher executive functions. Impaired executive function affects mental flexibility, planning, self-monitoring, and problem solving. The disorder can suppress otherabilities, such as attention and memory. After a period of post-traumatic amnesia (APT), patients with severe TBI may suffer from memory impairment of varying intensity and long-term impairment of short-term memory. Changes in behavior and personality can bessociated with TBI, such as reduced motivation and self-esteem, difficulty with empathy, processing emotions, psychosocial difficulties posttraumatic stress disorder, depression, anxiety, and fatigue.[15]

The locations most frequently involved in head injuries are the anterior, inferior, and lateral temporal lobes, as well as the frontal lobes.[14] There is involvement of neurotransmitter changes in neurobehavioral sequelae, including cognitive impairment. The changes that occur involve catecholamines, cholinergics, and serotonin. The frontal- subcortical area with its three main circuits plays an important role in the regulation of behavior. These areas overlap with areas prone to injury causing behavioral and emotional changes post-injury. Each circuit begins its journey from the frontal cortex and is projected sequentially to the striatum, globus pallidus, thalamus, and back to the frontal cortex. The circuits involved are:[18,22]

- The dorsolateral frontal/prefrontal-subcortical will impair executive functions such as memory, decision making, problem solving, and mental flexibility.
- Lateral orbitofrontal-subcortical will interfere with intuition, social behavior, andself-control mechanisms.
- Medial frontal-subcortical anterior will cause disturbances motivation and initiation.

The hippocampus plays a role in the formation of declarative memory indicating atrophy on MRI in patients with moderate to severe TBI. Moderate to severe TBI is thought to cause persistent and long-term cognitive impairment, whereas mild TBI is associated with short-term cognitive dysfunction that tends to improve within 3 months of injury. Recently, patients with mild TBI (up to 15%) will experience post-concussion syndrome, which results in persistent cognitive impairment along with other neurobehavioral symptoms such as emotional disturbances and headaches.[11]

The cognitive sequelae of TBI are determined by several variables, including: severity of TBI, complications, other injuries to other areas of the body, and chronicity of the injury. Patient characteristics such as age, previous neuropsychiatric status, and genotype also playa role. In addition, cognitive recovery from TBI may be affected by the quality of the post- injury environment. In general, the relationship between the severity of TBI and cognitive sequelae is linear with the length of duration of impaired consciousness predicting broader cognitive dysfunction. The heterogeneity in TBI pathology and patient characteristics also

affects cognitive outcomes, making predictions of recovery difficult. The cognitive domains most affected in mild-moderate TBI are memory, attention, information processing speed, and cognitive function and usually returns within 3-6 months of injury. Moderate to severe TBI is also associated with memory, attention, information processing speed, executive function, and also involves communication, visuospatial processing, and intellectual abilities.[6] Meta-analysis of 39 cross-sectional studies on the cognitive impact of mild to severe TBI, it was found that overall cognitive function will improve in the early weeks aftermild TBI and will return to baseline within 1-3 months. Cognitive function will also improvein the first 2 years after moderate and severe TBI, but is also found to be impaired in cases >2years after trauma.[2] This study lobes location brain injury not significant by analysis in two group for cognitive impairment that same with martin study.[18]

Based on the problem formulation and literature review, a framework can be developed. Traumatic intracranial hemorrhage is caused by traumatic brain injury. Intracranial hemorrhage volume is associated with glutamate excitoxicity, calcium overload, free radical formation, mitochondrial dysfunction, inflammation, and activation of pro-apoptotic genes.[1]

Through the mechanism brain injury with cognitive impairment at neuroinflammation, complement activation will occur followed by infiltration of neutrophils, monocytes, and lymphocytes that cross the blood brain barrier, then secrete prostaglandins, free radicals, proinflammatory cytokines (TNF, IL-1ß, IL-6, IL-12), and other inflammatory mediators which then increase the expression of chemokines and cell adhesion molecules, activate astrocytes and microglia, JNK, p38/MAPK, CaMKII, and ERK. The neuroinflammatory process will affect LTP and LTD, causing cell death so that it will resultin decreased hippocampal plasticity and cognitive impairment.

The limitation of this study is the short duration of the study. This study used subjects in certain populations in certain places; hence, this study's results cannot describe the same conditions in different populations and places. Further research is needed to improve this study's results using a larger sample size involving various types of cancer and using cohort research methods.

CONCLUSION

Bleeding volume in hemorrhagic TBI increased five times and GCS 9-13 increased 0.1 times decreased function cognitive cause of neuroinflammatory process will affect LTP andLTD, causing cell death so that it will result in decreased hippocampal plasticity and cognitive impairment when TBI.

Informed Consent and Patient Details

The authors declare that this research does not contain any personal information that could lead to the identification of the patient(s) and/or volunteers.

Declaration by Authors

Ethical Approval: The ethical permission in this study with No. 2349/UN 14.2.2VII.14/LT/2021 from the research ethics commission of the Faculty of Medicine, Udayana University/ Sanglah CentralGeneral Hospital Denpasar

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