REVIEW ARTICLE

Effect of Administration of Anti- Alzheimer Medications on Outcome of Patients with Traumatic Brain Injury

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ABSTRACT

Traumatic brain injury (TBI) presents a significant global health concern, with profound implications for both mortality and long-term disability, particularly among younger demographics. Despite advancements in intensive care management and the establishment of standardized protocols, mortality and morbidity rates among TBI patients remain alarmingly high. Current prognostic models, relying on demographic factors, clinical assessments, and radiological findings, often lack robust predictive capacity, necessitating exploration of alternative indicators for early outcome prediction in TBI cases. Inflammatory responses play a pivotal role in the pathophysiology of TBI, with rapid alterations observed in platelet count and function within minutes post-injury. Inflammatory cytokines, including high-sensitivity C-reactive protein (hsCRP) and tumor necrosis factor α (TNF-α), contribute to secondary inflammatory cascades, correlating with the progression of secondary brain injury. Many drugs are currently being evaluated as potential treatment for TBI. Though the exact mechanism is unknown, amantadine(memantine) as anti alzheimer medication appears to act as an NMDA receptor antagonist and an indirect dopamine agonist also Oxiracetam is a pro-intellectual drug used for mild-to-moderate vascular dementia, Alzheimer's disease, memory and intellectual impairment due to traumatic brain injury. Nonetheless, oxiracetam has been sporadically studied in the treatment of severe craniocerebral injury (Yazar et al.,2021).

Objective

Focusing on the impact of administration Anti- Alzheimer medications as memantine, oxiracetam and others on outcome of Patients with Traumatic Brain injury and their effect on neutrophil/lymphocyte ratio (NLR), C-reactive protein (CRP),platelet count in these patients.

Keyword: Traumatic brain injury (TBI); Oxiracetam ,memantine; neutrophil /lymphocyte ratio (NLR); TBI.

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INTRODUCTION

It has been observed that a growing number of injuries are associated with industrialization and the rapid growth of motorization,TBI is considered a heterogeneous disease with respect to cause, pathology, severity and prognosis, because TBI is a type of injury that becomes one of the leading causes of global morbidity, mortality, and socio-economic burden which caused by direct external mechanical force to the cranium and its intracranial components, causing disruption to the brain structure and function, which can be temporary or permanent in form of cognitive decline, neurodegenerative disease and increased risk of seizures and sensory disturbances (Williams et al.,2015). This causes considerable uncertainty in the expected outcome of individual patients. Globally, an estimated 10 million people will be affected annually by TBI. By 2020, TBI is projected to surpass many diseases as a major cause of death and disability (Bourget et al., 2022). The World Health Organization (WHO) predicted that road accidents alone, which account for the majority of TBI cases, will constitute the third-largest contributor to the global burden of disease and disability after heart disease and depression (Werner et al.,2015).

Definition of TBI

A traumatic brain injury is defined as a traumatically induced structural injury and/or physiological disruption of brain function as a result of an external force. It is indicated by new onset or worsening of at least one of the following clinical signs immediately following the event: Such as periods of consciousness loss or decreased consciousness, memory loss for events before or after the injury (posttraumatic amnesia), alterations in mental state at the time of injury such as confusion or disorientation, neurological deficits such as weakness or sensory loss, and the presence of intracranial lesions. These symptoms may vary in severity and duration and could potentially be ameliorated by the timely administration of medication that affect TBI outcome (Begemann et al., 2020).

Epidemiology and Impact

Traumatic brain injury (TBI) is a serious public health issue leading to death and disability . The rates of TBI in different sex and age groups vary. The age groups associated with

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Head Trauma – Glasgow Coma Scale					
Eye Opening					
Spontaneous 4	To speech 3	To pain 2	None 1		
Verbal Responses					
Orientated 5	Confused conversation 4	Inappropriate words 3	Incomprehensible sounds 2	None 1	
Best motor responses – When there is right/left or upper/lower asymmetry use the best motor response to calculate the score as this is the best predictor of outcome					
Obeys Commands 6	Localizes pain with purposeful movements 5	Flexion withdrawal to pain 4	Abnormal flexion (decorticate) 3	Extension (decorticate) 2	None (flaccid) 1

Figure 1: The individual score of different response of GCS. (DiBona et al., 2021)

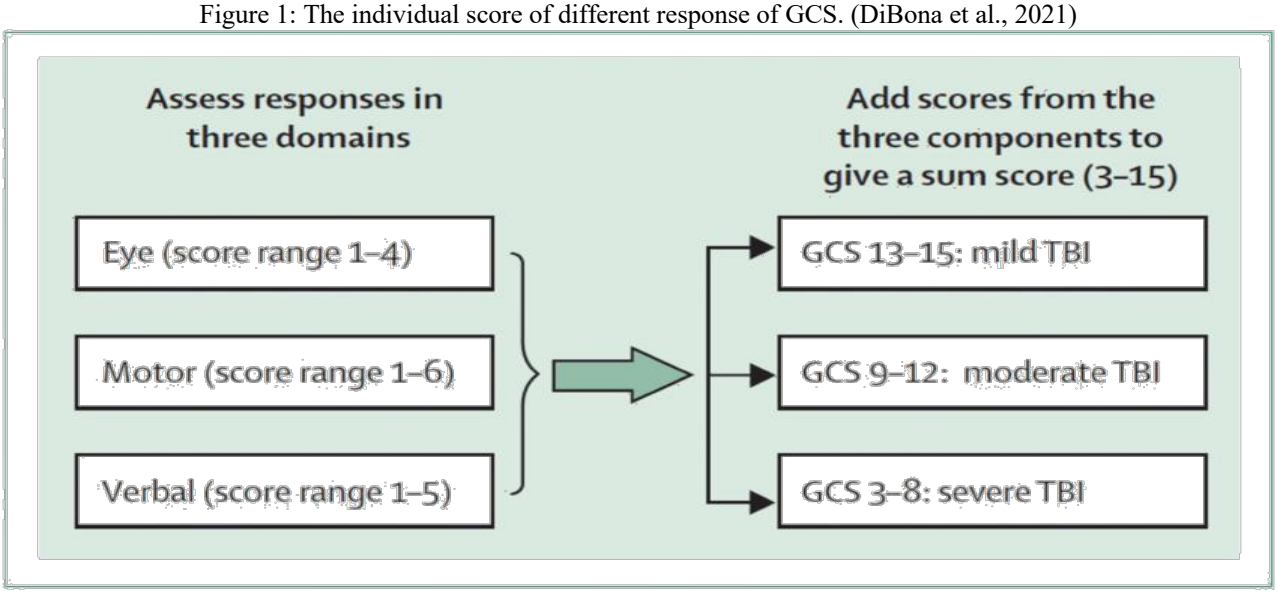

Figure 2: The severity group of the patient after summing the individual response score. (DiBona et al., 2021)

the highest rates of emergency department visits, hospitalization and deaths are young children aged 0 to 4 years, individuals aged 15 to 24 years, and seniors aged 75 years or older . Males have a 1.4 times higher incidence of TBI than females across all age groups . For all age groups, TBI most commonly results from falls, motor accidents, or being struck by an object ,The World Health Organization (WHO) estimates that almost 90 % of deaths are trauma related in low-and middle-income countries. Across all ages, TBI is one of the main causes of trauma-related deaths, and the leading cause of disability under forty-year-old's . Consequently, it is recognized as a major socioeconomic problem throughout the world, where the injuries are not only causing health-loss and disability for individuals and their families, but also contributes to an increased burden on the health-care systems due to high health-care costs (Bhatti et al., 2018).

Classification of TBI

Traumatic brain injuries are categorized based on their severity, with mild, moderate, and severe classifications. In cases of mild TBI, the individual typically remains alert

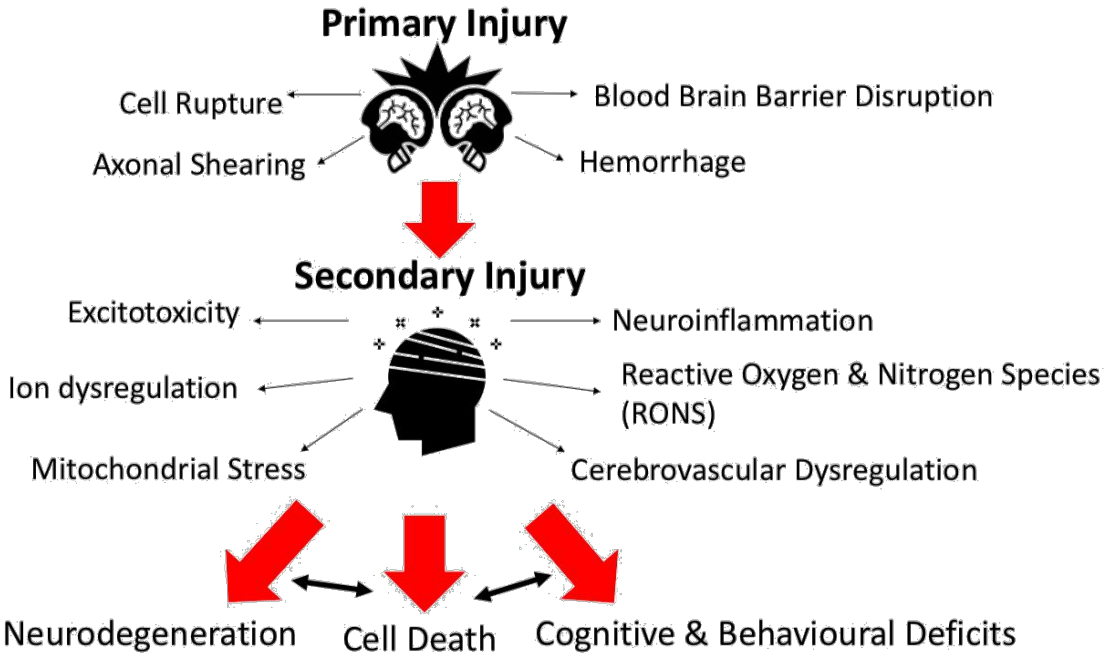

Figure 3: Downstream Primary and Secondary Injury Cascades. Summary of secondary injury mechanisms accompanying initial primary injury, responsible for long term impairments. (Hier et al., 2021)

with their eyes open, although symptoms such as confusion, disorientation, memory loss, headache, and momentary loss of consciousness may occur. Moderate TBI results in lethargy, with eyes opening only in response to stimulation. Unconsciousness may persist for a period ranging from 20 minutes to 6 hours, often accompanied by brain swelling or bleeding, leading to a disturbed sleep pattern and significant pain. Severe TBI is characterized by unconsciousness, with eyes remaining closed even when stimulated, and unconsciousness lasting for more than 6 hours (Rogers et al.,2017).

Clinical Evaluation of TBI

Any person with signs of moderate or severe TBI should receive medical attention as early as possible. Because we cannot do much to reverse the initial brain damage caused by trauma (Chen et al., 2019). Measuring TBI Severity: The Glasgow Coma Scale (figure 1&2) The Glasgow Coma Scale (GCS) is used to grade TBIs of adults on a 15 point scale and categorizes cases as mild , moderate , or severe . The GCS is a sum of three separate measures: degree of eye opening , verbal capacity , and motor response . The severity of TBI approximately reflects the patient's level of consciousness. This is a quick and standardized measurement and is routinely used in emergency rooms (Clark et al., 2017).

Eye Opening Response

The GCS tests patient eye-opening response because having the ability to open eyes in response to certain stimuli indicates that patient cerebral cortex is processing information. The inability to open eyes suggests damaged cerebral cortex. There are four grades for this part of the test.

Verbal Response

Speaking skills indicate that patient have integration with your central nervous system. That means patient can process information from environment and then respond. There are five grades for this part of the test. The points given for each type of verbal response after a head injury. (Dewan et al., 2018)

Motor Response

Having a motor response is a sign that patient central nervous system is working. The examiner will test motor response in patient arms as arms present a wider range of response (DiBona et al., 2021).

Pathophysiology of TBI

There are two pathologic processes that occur in TBI ,The first is primary brain injury, which caused by mechanical force exposure to the brain tissue, causing axonal, glial cells, and vascular damages of the brain tissue. Those damaged brain cells then can initiate the second pathologic process in TBI by releasing various inflammatory factors and neurotransmitters that can initiate and develop the inflammatory cascade, thus causing neuroinflammation and aggravate the brain injury, which called secondary brain injury (SBI). This SBI can lead to more severe morbidities such as motoric, cognitive, and psychological disturbances that can be suffered by the patients for the rest of their lives, or even death. Thus, an inflammatory biomarker that can reflect the neuroinflammation and SBI severity post-TBI is needed to increase the effectivity of TBI patient management and prevent the morbidity and mortality caused by SBI post-TBI. The levels of inflammatory reactions that occur in the body can be reflected from increased inflammatory cell count, such as neutrophils and platelets, or increased inflammatory biomarker levels, such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). CRP and ESR are commonly used by medical practitioners to help them in monitoring the progression of inflammatory diseases. However, CRP and ESR are barely used in traumatic cases, especially in SBI post-TBI. On the

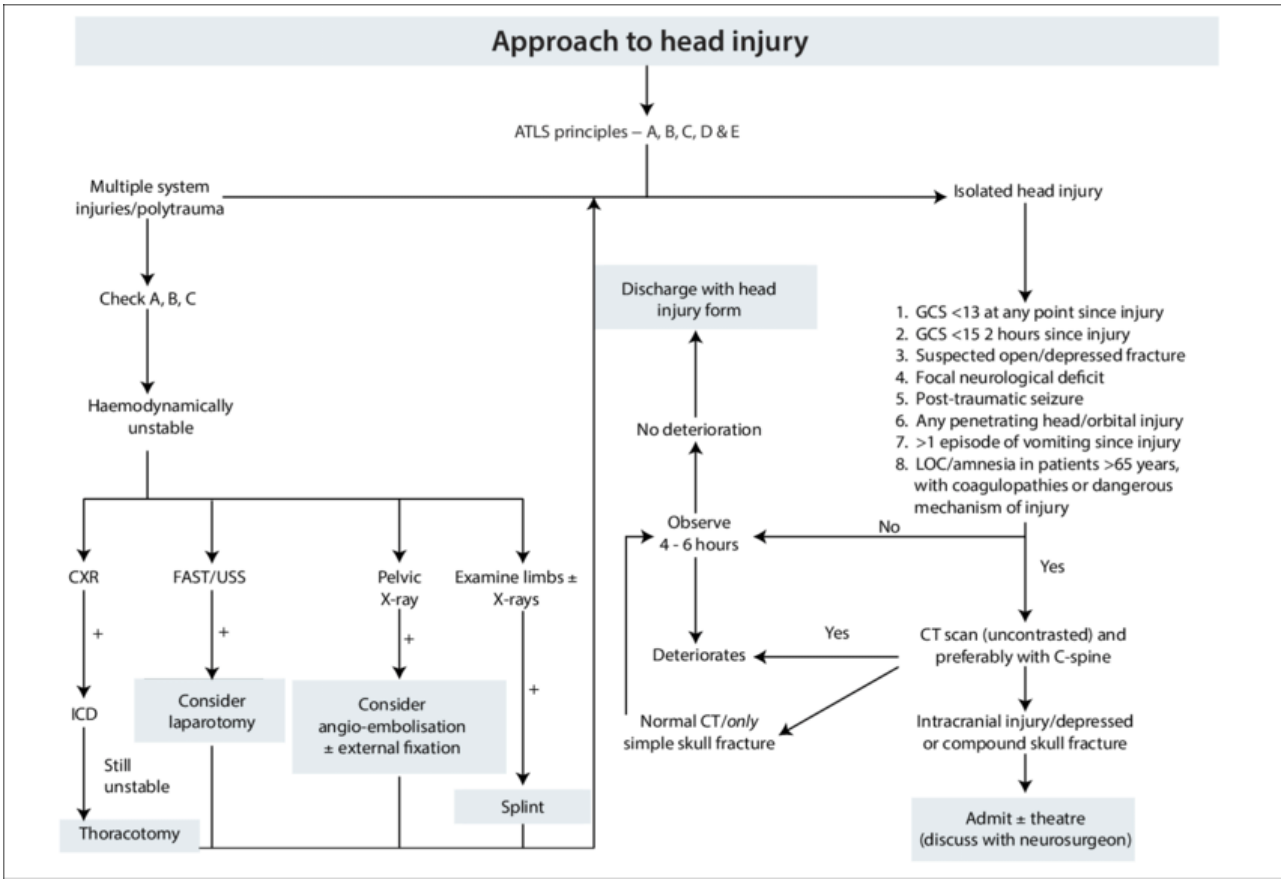

Figure 4 : Approach to head injury (SAMJ ; 2015).

other hand,further studies showed that neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) could act as a promising inflammatory biomarker and very easy to be measured. NLR and PLR can be obtained from the complete blood count (CBC) examination, which is more routinely done compared to CRP and ESR in traumatic case management, especially TBI. The CBC examination also more available and affordable in every hospital, including in primary health care in rural areas. The CBC examination is a simple laboratory test and can provide several important data at once about the markers that can be useful in daily medical practice (Akboga et al.,2016). Thus, the CBC is recommended to be done before carrying out other laboratory tests that are more expensive and invasive. NLR and PLR have the potential to be used as a marker of the serious bacterial infection (SBI) severity post-TBI. Therefore, this review article was conducted to correlate PLR results with the CRP and NSE results of TBI patients as the marker of the inflammatory process and SBI severity post-TBI. It is hoped that NLR and PLR can become a useful and more affordable marker for predicting the severity of inflammatory processes and SBI post-TBI. Thus, more effective SBI monitoring to alert and prevent the clinical deterioration, morbidities, and mortality of TBI The neutrophil-to-lymphocyte ratio (NLR) has good generalizability and can be calculated and obtained from routine laboratory tests at admission without further inconveniencing the patient. Studies have shown that the NLR is associated with the inflammatory response, with a patients can be done after anti alzhiemer medication are given. Excitotoxicity and apoptosis occur after TBI are two mechanisms of neuronal cell death that occur in TBI and are mediated through the N-methyl-D-aspartate (NMDA)-type glutamate receptor (Wang et al .,2018). The N-methyl-D-aspartate (NMDA)-type glutamate receptors implicated in both mechanisms. With moderate hyperactivity of glutamate receptors, there is an excessive influx of calcium (Ca2+) which leads to apoptosis (programmed cell death),Whereas, in excitotoxicity, there is a massive release of glutamate resulting in the loss of Mg2+ within the glutamate receptor's ion channel. Without the regulating effect of Mg2+, there is an influx of calcium and sodium, which causes the neuronal cells to depolarize, swell and lyse (necrosis). With necrosis, there is a release of cellular contents that leads to neighbouring neuronal dysfunction or neuronal cell death by excitotoxicity. Neuronal dysfunction occurs secondary to ischemia caused by the increased energy demands needed to maintain ion gradients. Similarly, activation of NMDA receptors by glutamate promotes the production of reactive oxygen species (ROS) and nitric oxide (NO) which further exacerbate secondary cell injury (Figure3).

The neutrophil-to-lymphocyte ratio (NLR) & platelet-to-lymphocyte ratio(PLR) As Inflammatory Markers:

higher NLR indicating poorer prognosis for patients with chronic obstructive pulmonary disease, myocardial infarction, and sepsis. Moreover, a previous study showed that the NLR was associated with the neurologic outcome in intracranial hemorrhage. As the NLR is routinely

measured in clinical laboratories as a component of the complete blood count (CBC) and is available to most patients, it can be very useful for risk stratification in clinical decision-making. Therefore, the NLR would help to predict the outcome of elderly patients with severe trauma who visited the emergency department (ED). Also the relationship between the PLR and in-hospital mortality in elderly patients with severe trauma have been examined (Hier et al., 2021). TBI patients need to supplement colloidal solution in time to maintain an average and reasonable arterial blood pressure, and they shall also properly control the blood glucose concentration. In addition, the sugary liquid should not be used to avoid postoperative PLT , NLR and PLR abnormalities+ (Hutchinson et al., 2015). Based on the GCS scores of TBI patients, some studies divided them into mild, moderate and severe groups. By comparison, the results showed that TBI patients had significantly lower PLT level but significantly higher NLR than the healthy subjects, especially those in the severe group with more obvious differences. These results indicated that PLT level and NLR were abnormal in patients with craniocerebral trauma, which was related to the severity of injury. After craniocerebral trauma, a large number of platelets are adhered to the constricted vessels and aggregated to participate in the coagulation, finally inducing thrombus . There-fore, the low PLT level in TBI patients may be caused by the heavy consumption of platelets in the body (Chen et al., 2019). Low NLR is mainly achieved by decreasing neutrophil count and increasing lymphocyte count. The primary injury mechanism of TBI leads to the rupture of capillaries and vessels and the destruction of the blood–brain barrier (BBB), triggering the interaction between platelets and endothelial cells or subendothelial matrix. This results in platelet adhesion-activation, and the formation of platelet embolism at the injury site for hemostasis. The balance between coagulation and anticoagulation is broken in moderate to severe TBI patients, leading to platelet overactivation and the number decreases at the early stage of injury. The spontaneous aggregation and subsequent excessive consumption induce secondary platelet depletion and increase bleeding risk. Studies had shown the increasing risk of intracranial hemorrhage progression when the platelet was less than 175,000/mm, and nine-fold higher mortality when the number is below 100,000/mm (Reith et al., 2017).

Correlation of NLR and PLR with CRP and ESR in TBI patients

Studies found that NLR and PLR were positively correlated with CRP in TBI patients. This could occur because the neuron and glial cells damaged by TBI can release various inflammatory cytokines and neurotransmitters, such as IL-1β, TNF-α and IL-6 to induce the inflammatory cascade response and develop neuroinflammation. These inflammatory cytokines can cause neutrophils and platelets activation, increase thrombopoiesis, and increase the CRP levels,the increase of NLR and PLR levels indicate increased cellular damage, BBB damages, neuroinflammation process, and cerebral edema, thus reflecting a more severe SBI post-TBI . Furthermore, CRP levels are doubled every 8-h and peak within 36–50-h after the onset of TBI . Since the NLR, PLR, and CRP are increased rapidly post-TBI so that the NLR and PLR results on the 1-day post-TBI can have a positive correlation with CRP results on the 1-day post-TBI in TBI patients (Chen et al., 2019). Studies found that NLR and PLR were not correlated with ESR in TBI patients. This could occur because the CBC and ESR examinations were carried out on the 1-day post-TBI, where the ESR levels do not change rapidly at the beginning of the inflammatory process and return to normal range in a longer time than other acute phase reactants, while NLR levels can increase rapidly post-TBI, and PLR levels also have not increased significantly. ESR begins to increase within 24–48-h after the onset of inflammation (slower than CRP), then gradually decreases after the inflammation subsides. Therefore, ESR is considered as a better marker for clinical monitoring over the course of the disease over time and for chronic inflammatory diseases. Maybe it would be better if the blood examinations were carried out on the 3-day post-TBI to assess the correlation between NLR and PLR with ESR in TBI patients, where the ESR levels had already begun to increase, and the lymphocytes count would experience a more significant decrease so that it could affect the PLR results in TBI patients (Halbgebauer et al., 2022).

Outcome Of TBI Patients

The complex and heterogeneous nature of brain injury renders predicting outcomes challenging across the TBI spectrum, particularly for patients with more severe injuries. This challenge most often falls on critical care professionals charged with counseling families to make vital decisions, including whether to continue or withdraw life-sustaining treatment, based on information they believe is relevant to anticipating long-term functional outcomes. Many studies have reported that, during the acute phase, trauma specialists overestimate the likelihood of poor outcome and underestimate the probability of good outcome in patients with severe injuries. Those clinician biases often influence key decision-making about patient care, even within the first 24 hours of injury. The vegetative state (VS) is generally viewed as a dire outcome and an influential driver in clinical decision-making and goals of care. Greater knowledge of the natural history of recovery from traumatic vegetative state (VS) is critically important to clinical practice in combating the pervasive nihilism associated with this diagnosis. It is essential that clinicians, particularly those in neurocritical care, recognize that traumatic vegetative state (VS) is a dynamic condition that evolves over the first year. Many evidences suggest that key behavioral benchmarks presaging later recovery often do not emerge in patients with traumatic disorders of consciousness until after 6 weeks post injury (Giacino et al; 2020). Withdrawal of life-sustaining treatment based on early prognostication of poor outcome accounts for most deaths in patients hospitalized for severe TBI. In view of existing evidence, the recently published American Academy of Neurology–American Congress of Rehabilitation Medicine–National Institute on Disability, Independent Living, and Rehabilitation Research Practice

Guidelines on Disorders of Consciousness strongly recommended that clinicians avoid statements suggesting that patients with disorders of consciousness who are within 28 days of injury have a universally poor prognosis (Giacino et al; 2018).

Treatment and Diagnosis

Patients with severe and moderate TBI should follow ATLS protocol *(figure 4)* with the main goal is to reduce or prevent of secondary brain insults that are known to worsen outcome after TBI. Hypotension and hypoxia are known to be main reasons of risk indicators should be managed probably. Early emergency surgery after head injury should be considered and are based upon neurologic findings and TBI treatment recommendations in points (Roozenbeek et al;2017).

1) Decompressive craniectomy

Bifrontal DC is not recommended to improve outcomes as measured by(The Galscow Outcome Scale-Extended) GOS-E score at 6 monthes post-injury in severe TBI patients with diffuse injury (without mass lesions), and with ICP elevation to values >20 mm Hg for more than 15 min within a 1-h period that are refractory to first-tier therapies. However, this procedure has been demonstrated to reduce ICP and to minimize days in the ICU.

• A large fronto temporoparietal DC (not less than 12 x 15 cm or 15 cm diameter) is recommended over a small fronto temporoparietal DC for reduced mortality and improved neurologic outcomes in patients with severe TBI.

2) Prophylactic hypothermia

• Early (within 2.5 h), short-term (48 h post-injury), prophylactic hypothermia is not recommended to improve outcomes in patients with diffuse injury.

3) Hyperosmolar therapy

Mannitol is effective for control of raised ICP at doses of 0.25 to 1 g/kg body weight. Arterial hypotension (systolic blood pressure <90 mm Hg) should be avoided.

Restrict mannitol use prior to ICP monitoring to patients with signs of trans tentorial herniation or progressive neurologic deterioration not attributable to extracranial causes.

4) Cerebrospinal fluid drainage

• An EVD system zeroed at the midbrain with continuous drainage of CSF may be considered to lower ICP burden more effectively than intermittent use.

• Use of CSF drainage to lower ICP in patients with an initial GCS <6 during the first 12 h after injury may be considered.

5) Ventilation therapies

• Prolonged prophylactic hyperventilation with $PaCO_2$ of ≤25 mm Hg is not recommended.

•Recommendations from the prior (Third) Edition not supported by evidence meeting current standards.

Anti-Alzheimer Medications And Their Use In TBI Patients (Jens et al,2022).

Anti-Dementia Drugs Examples

Reversible Acetylcholinesterase Inhibitors (AChE-I)

Taking into account that there is a significant cholinergic deficit in the beginning of AD, using AChE-I is a reasonable starting point to fight against that cholinergic deficit in early stages of AD. Therefore, the synaptic

status in head CT such as large hematoma volume or evidence of mass impact including midline shift. There is a lag in the improper triaging and transfer of patients . The referral systems need counseling and revision with administrative health authorities to improve these parameters and subsequently improv transferred to tertiary hospitals directly which have the facilities to deal with patients of head trauma (SAMJ ; 2015). Bed sores are serious complications that frequently develop in patients with severe traumatic brain injury. Bed restriction predisposes risk factors to the development of pressure injuries and thromboembolic events in those critically ill patients (Borghardt et al; 2016).

•Hyperventilation is recommended as a temporizing measure for the reduction of elevated ICP.

•If hyperventilation is used, SjO_2 or $BtpO_2$ measurements are recommended to monitor oxygen delivery.

6) Anesthetics, analgesics

• Administration of barbiturates to induce burst suppression measured by EEG as prophylaxis against the development of intracranial hypertension is not recommended.

• High-dose barbiturate administration is recommended to control elevated ICP refractory to maximum standard medical and surgical treatment. Hemodynamic stability is essential before and during barbiturate therapy.

•Although propofol is recommended for the control of ICP, it is not recommended for improvement in mortality or6-month outcomes. Caution is required as high-dose propofol can produce significant morbidity.

7) Steroids

• The use of steroids is not recommended for improving outcome or reducing ICP. In patients with severe TBI, high-dose methylprednisolone was associated with increased mortality and is contraindicated.

8) Nutrition

• Feeding patients to attain basal caloric replacement at least by the fifth day and at most by the seventh day post-injury is recommended to decrease mortality.

• Transgastric jejunal feeding is recommended to reduce the incidence of ventilator-associated pneumonia.

9) Infection prophylaxis

• Early tracheostomy is recommended to reduce mechanical ventilation days when the overall benefit is thought to outweigh the complications associated with such a procedure. However, there is no evidence that early tracheostomy reduces mortality or the rate of nosocomial pneumonia.

• The use of Povidone iodine oral care is not recommended to reduce ventilator-associated pneumonia and may cause an increased risk of acute respiratory distress syndrome.

degradation of acetylcholine (ACh) by hydrolysis into choline and acetate is inhibited, which increases Ach availability within the synaptic cleft. Earlier approaches tried adding ACh precursors (phosphatidylcholine or diethylaminoethanol) or cholinergic agonists (M1 receptor agonists). They did not prove to be as clinically efficient as the one regarding AChE_I. The first marketed AChE-I was Tacrin which was removed from the market due to severe

hepatotoxicity. Until today, there are three reversible AChE-Is available donepezil, rivastigmine, and galantamine. For ChE-Is, treatment starts by minimal doses and usually requires slow up-titration for weeks until the maximum dose has been reached. In terms of pharmacokinetic interactions of the three AChE-Is donepezil, galantamine, and rivastigmine, only donepezil and galantamine possess an affinity to the cytochrome CYP450 isoenzymes CYP-2D6 and CYP-3A4, while Rivastigmine is hydrolyzed and then its components are excreted by the kidneys. Donepezil and galantamine also bear the risk of QTc-prolongation, which could potentially lead to torsade de pointes of the heart, a severe kind of ventricular tachycardia. Further, patients suffering from COPD should only be treated by AChE-I with caution. Since all AChE-I functionally inhibit ACh degradation, they share a wide range of side effects – nausea, diarrhea, and reduced appetite above all. Vertigo and cephalgia sometimes occur. Rivastigmine uses the identical binding site of AChE as ACh, its hydrolysis takes much longer and therefore leads to a temporary blockade of AChE. Rivastigmine is an alternative to oral administration which is also available as adhesive transdermal
patch allocating continuous release of the remedy over 24 h.

Galantamine and Donepezil

Donepezil and galantamine bind to different sites on AChE and they are metabolized by the hepatic cytochrome HCYP450 enzyme complex causing pharmacokinetic interactions. In addition to the regular function of AChE-I, galantamine further impacts on cholinergic neurotransmission by modulating nicotinergic receptors pre- and post-synaptically while Rivastigmine inhibits butyrylcholinesterase in addition.

Memantine

Overactivation of glutamate receptors, especially NMDA-type receptors, lead to an excess of calcium influx into neurons causing neurotoxic effects. Memantine is a noncompetitive NMDA receptor antagonist. In fact, it is almost a modulator at the NMDA receptor, since it does not interact with the glutamate binding site. The interaction itself is use dependent and it takes place inside the NMDA receptor at a magnesium binding site. This is possible only after activation of the ionic channel ,Memantine rapidly diffuses from this binding site. As a consequence, it does not inhibit the ionic channel for a long time. In general, the neurotoxic effect of glutamate on the ionic channel is blocked without blocking the synaptic effects of glutamate on cognitive function. Neuroplastic effects attributed to memantine are additionally caused by its impact on mitochondrial functionality. Prescribing memantine usually starts after the initial stage of AD when the patient
starts to show BPSD (behavioral and psychological symptoms of dementia) and continues to deteriorate cognitively. Memantine is an oral medication, which is rapidly absorbed and it is excreted renally. Its half-life is 50–100 h time period.

Treatment regime begins at 5 mg p.o. for a week. The dose is augmented by 5 mg every week until the final dose of 20 mg has been obtained within a month. Due to severe nightmares caused by memantine, it should be taken in the morning.

In the case of kidney disease, daily doses should be adjusted. Since memantine impacts on cerebral epilepsies, it should be avoided in epileptic patients. Side effects include dizziness, headache, diarrhea, constipation, confusion, seizures (rare), allergic reactions, nausea, abdominal pain, change in mental health, and congestive heart failure. Cephalgia, vertigo, dyspnea, and elevated liver transaminases have also been reported as undesired side effects. Contraindications include renal impairment, hepatic disturbances, pregnancy, lactation, children, and infants.

Nootropic Drugs (ND)

Nootropic drugs is a generic term for drugs without a distinct function in the CNS, which still influence cognitive function. ND include nicergoline, piracetam, and pyritinol. Although they have a large variety of functional mechanism, they still lack clinical evidence for being effective as antidementive medication. Considering side effects and the lack of clinical benefit, ND should be avoided in treating AD and have only limited effects in the treatment of AD or vascular dementia.

Piracetam

Side effects associated with piracetam are diarrhea, weight gain, drowsiness, insomnia, nervousness, depression, muscle spasm, and hyperactivity. Contraindications are hepatic impairment, renal impairment, pregnancy lactation, hemorrhagic diasthesis, and Huntington's chorea. Interactions: There are no severe or serious interactions with other drugs. Moderate interactions have been noted for cilostazol, clopidogrel, dipyridomole, eptifibatide, prasugrel, ticlopidine, and tirofiban. Mild interactions have been noted for levothyroxine, liothyromine, and thyroid desiccated.

Oxiracetam

Allevate Anti-Inflammatory Activity And Ameliorate Cognitive Imparement At Early Phase OF TBI: Oxiracetam is a water-soluble ampakine nootropic in the racetam-family of compounds. It was the 3rd racetam nootropic to be developed.

Oxiracetam modulates both Alpha-amino 3-hydroxy 5-methyl 4-isoxazolepropionic acid (AMPA) and N-methyl D-aspartate (NMDA) receptors which prevents the glutamate toxicity associated with TBI. It also seems to prevent an imbalance of acetylcholine activity which should also benefit those recovering from brain injury. Oxiracetam enhances protein kinase C (PKC) which affects M1 acetylcholine receptors. Oxiracetam even demonstrates the ability to repair these receptors when damaged. Such as from traumatic brain injury Recommended dosage of Oxiracetam is 750 – 1,500 mg per day split into two doses. Since this nootropic boosts acetylcholine in your brain, you should stack it with a good choline source like Alpha GPC or CDP-Choline. (Liu et al.,2013)

CONCLUSION

traumatic brain injury (TBI) remains a significant public health concern globally, contributing to substantial morbidity and mortality rates, especially among young

adults. Inflammatory responses play a crucial role in TBI pathophysiology, with rapid alterations in platelet count and function observed post-injury. Inflammatory cytokines such as high-sensitivity C-reactive protein (hsCRP) and tumor necrosis factor α (TNF-α) contribute to secondary inflammatory cascades, exacerbating the progression of secondary brain injury so outcome may be predicted by measuring PLR , NLR and their correlation with NSE (neuro specific enolase enzyme) but more easily done and less expensive and easily available. Furthermore, pharmacological interventions, including usage of anti-alzheimer medicatios as memantint , oxiracetam and others hold potential for neuroprotection in TBI management. Previous studies have demonstrated encouraging short-term effects of oxiracetam on neurological function emphasizing its potential as a therapeutic agent . Despite advancements in critical care management, current prognostic models for TBI lack robust predictive capacity, highlighting the need for alternative indicators to inform early outcome prediction.

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