



EFFICACY OF ANTICONVULSANT ADMINISTRATION AS A SEIZURE PROPHYLACTIC THERAPY IN TRAUMATIC BRAIN INJURY PATIENTS

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KEYWORDS	ABSTRACT
traumatic brain injury, anticonvulsant, prophylactic therapy.	Traumatic brain injury (TBI) is a non-degenerative, non-congenital disorder of the brain that occurs due to external mechanics that can cause permanent or temporary impairment of cognitive, physical and psychosocial functions. Based on the 2018 Basic Health Research (Riskesdas) data, the prevalence of head injuries in Indonesia is 11.9%. Seizures after head injury result in secondary brain damage and seizure prophylaxis is only recommended in patients with TBI during the first seven days. This study was designed to assess the efficacy of anticonvulsants as prophylactic therapy in patients with TBI in Indonesia. The research method used was a literature review that was searched using Google Scholar, Pubmed, Medline, Ebsco, Hindawi, ScienceDirect, and Cochrane, published in the last ten years. After obtaining the appropriate literature, the manuscript is written. The results showed that prophylactic anticonvulsants such as Phenytoin could reduce the incidence of early posttraumatic seizures (PTS) in patients with TBI compared to placebo. Another study also stated that giving anticonvulsants (Carbamazepine, Phenobarbital, Phenytoin, Levetiracetam and Valproate) in preventing early PTS showed effective results in TBI when compared to placebo. So, it can be concluded, based on the literature search conducted, anticonvulsants are proven to be able to prevent PTS, with the recommendation of drug choice being Phenytoin.

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INTRODUCTION

Traumatic brain injury (TBI) is a non-degenerative, non-congenital disorder of the brain that occurs due to external mechanics that can cause permanent or temporary impairment of cognitive, physical and psychosocial functioning (Dawodu, 2021). Traumatic brain injury can be caused by a collision, blow or jolt to the head or a penetrating head injury that disrupts the brain's normal function (Capizzi et al., 2020). The Centers for Disease Control and Prevention (CDC) stated that 2014 there were 2.53 million emergency room visits with TBI cases. Adults aged 75 years and over had the highest rate of TBI-related Emergency Room visits (1682 per 100,000 people), followed by young children aged 0 to 4 years (1618.6 per 100,000 people) and lastly followed by adolescents and young adults aged 15 to 24 years (1010.1 per 100,000 people) (Capizzi et al., 2020). An epidemiological study by Dewan et al. states that an estimated sixty-nine million people suffer from TBI from all causes yearly, with the Southeast Asia and West Pacific regions experiencing the most significant overall disease burden (Dewan et al., 2018). Basic Health Research 2018 The prevalence of head injuries in Indonesia is 11.9%, with the highest prevalence in Papua (16.5%) and the lowest in South Kalimantan (8.6%) (Ministry of Health, 2018). Everyone has a risk of developing TBI, but certain groups are more vulnerable, such as older adults, women exposed to intimate partner violence, the homeless population, prisons and workers in high-risk jobs (Mollayeva et al., 2018).

The Brain Trauma Foundation and the American Academy of Neurology recommend prophylactic use of anticonvulsants to reduce the incidence of early posttraumatic seizures within seven days after TBI. This recommendation is based on the literature showing that prophylaxis with Phenytoin effectively reduces the risk of early posttraumatic seizures but may not effectively reduce the risk of late posttraumatic seizures (PTS) (Zimmermann et al., 2016). Research conducted by Kirmani et al. also stated that Phenytoin be the anticonvulsant of choice because it is widely studied and researched compared to other anticonvulsants, but further prospective clinical trials are needed regarding Phenytoin to prove its efficacy as a first-line agent in PTS (Kirmani et al., 2016). This study aimed to assess the efficacy of anticonvulsants as prophylactic therapy in patients with TBI in Indonesia, sehingga dapat diketahui langkah yang tepat untuk pemberian profilaksis pada pasien *traumatic brain injury*.

METHODS

The research design used in writing this journal is to use a literature review method related to the definition, epidemiology, predisposition, or risk factors for traumatic brain injury with the keywords traumatic brain injury, anticonvulsant, and prophylactic therapy. The literature sources that the authors use include Google Scholar, Pubmed, Medline, Ebsco, Hindawi, ScienceDirect, and Cochrane, which were published in the last ten years. We restricted the included studies to English language and adults post traumatic brain injury after undergoing hospitalized. Any types of articles were included, except an abstract-only publication and those that did not report the outcome of interest. Based on the search results, journal selection was carried out, and journals that met the criteria were obtained. The author then reviews each journal that meets the criteria and then writes literature.

RESULTS AND DISCUSSION

Traumatic Brain Injury

Traumatic Brain Injury is a non-degenerative, non-congenital disorder of the brain that occurs due to external mechanics that can cause permanent or temporary impairment of cognitive, physical and psychosocial functioning (Dawodu, 2021). Traumatic Brain Injury is divided into two categories, namely penetration and non-penetration. Penetrating traumatic brain injury occurs when an object penetrates the brain and enters the brain tissue. At the same time, non-penetrating TBI is caused by an external force strong enough to cause trauma to the part of the brain inside the skull (National Institute of Neurological Disorders and Stroke, 2023).

Traumatic Brain Injury is a case that is often found in the emergency room. Based on data from the CDC, in 2014 there were around 288,000 cases, and 56,800 of them died. Adults aged 75 years and over had the highest TBI-related ED visit rate (1682 per 100,000 people), followed by young children aged 0 to 4 years (1618.6 per 100,000 people) and lastly followed by adolescents and young adults aged 15 to 24 years (1010.1 per 100,000 people) (Capizzi et al., 2020). An epidemiological study by Dewan et al. states that an estimated sixty-nine million people suffer from TBI from all causes yearly, with the Southeast Asia and West Pacific regions experiencing the largest overall disease burden (Dewan et al., 2018). Basic health research in 2018, the prevalence of head injuries in Indonesia is 11.9%, with the highest prevalence in Papua (16.5%) and the lowest in South Kalimantan (8.6%) (Ministry of Health, 2018). Everyone has a risk of experiencing TBI, but groups of adults, women who experience domestic violence, the homeless population and workers in high-risk jobs are at greater risk of experiencing TBI (Mollayeva et al., 2018).

The most common complication of TBI is the occurrence of posttraumatic seizures. As many as 20% of patients in the Intensive Care Unit (ICU) and 25% -50% outside the ICU have post-TBI seizures (Zimmermann et al., 2016). Posttraumatic seizures are classified into early onset, which occurs from 0-

7 days after trauma, and late-onset, which occurs after seven days post-trauma, usually occurring in patients with moderate or severe TBI (Wat et al., 2019). A theory explains the mechanism of post-TBI seizures using animal models. The first posttraumatic day occurs with microRNA disruption, facilitating the transition to seizure activity. Disrupted microRNA exacerbates glutamate-mediated excitotoxicity after trauma. The induction of glutamate toxicity can be regulated by releasing iron from damaged blood cells that diffuse across the disturbed blood-brain barrier. The remaining neurons will participate in functional and structural adaptations, such as axonal growth, to increase the risk of subsequent hyperexcitability. Concomitant with changes in glutamate, a substantial reduction in GABA-releasing interneurons in the hippocampus leads to enhanced disinhibition time early posttraumatic (Lucke-Wold et al., 2015).

Another theory suggests that after TBI, the neuroinflammatory response is initiated rapidly, and the neuroinflammatory response has a pro-epileptogenic role in developing PTE. In general, after TBI, inflammatory cytokines, chemokines and complement proteins are rapidly released. This immune response signals various cellular mediators and initiates the acute phase response. Following this signal, astrocytes and microglial cells are induced to become active, multiply and migrate to the site of injury. Peripheral immune cells are also known to travel to the brain in response to TBI. Once this immune or neuroimmune response is activated to re-establish tissue homeostasis, these immune cells remove remnants and identify signalling potential pathogens. While the most intense neuroinflammatory responses occur relatively early (within hours and days after the trauma), low-grade neuroinflammation often persists chronically. Several early neuropathology reports acknowledged that progressive gliosis at the site of brain trauma is a significant component of the development of an epileptogenic focus (Mukherjee et al., 2020).

Days after injury, the damaged brain area can initiate a response consisting of a series of injury cascades that interrupt normal homeostasis. Part of this response depends on the mechanistic target of rapamycin (mTOR) which is thought to contribute to tissue damage and subsequent excitotoxicity. Mechanistic targets of rapamycin, in particular, have been implicated in PTE pathology. Acute neuroinflammation activates Akt, which phosphorylates mTOR and contributes to cell death. Toll-like receptors mediate another critical subacute response. Toll-like receptors trigger the innate immune system and regulate non-NMDA glutamate channels. Following trauma, activation of this toll-like receptor can lead to glutamate excitotoxicity that persists for several weeks. Toll-like receptor four is associated with temporal lobe spasms after trauma (Lucke-Wold et al., 2015).

Anticonvulsant as Seizure Prophylaxis in TBI Patients

Seizures after head injury result in secondary brain damage, which includes increased intracranial pressure, increased brain metabolic demands after head trauma and excessive release of neurotransmitters resulting in more severe damage. The use of anticonvulsants is to minimize brain damage by preventing early onset PTS (Kirmani et al., 2016). The Brain Trauma Foundation and the American Academy of Neurology for the Management of Severe TBI state that seizure prophylaxis is only recommended for patients who experience TBI during the first seven days (Zimmermann et al., 2016). The recommended seizure prophylaxis for TBI patients is Phenytoin. Phenytoin is more effective than other anticonvulsants in preventing the risk of early-onset PTS. However, it may not effectively reduce the risk of late-onset PTS (Wat et al., 2019).

Other anticonvulsants, such as Phenobarbital, Valproate and Carbamazepine, have not been extensively studied. Considering their side effect profile and pharmacodynamic properties, it can be concluded that there is no advantage of using these agents compared to Phenytoin (Torbic et al., 2013). Anticonvulsants that have a neuroprotective effect (Phenytoin) work by blocking voltage-dependent membrane sodium channels, which are responsible for increasing the action potential. Through this way

of working, anticonvulsants can block the positive feedback that maintains high-frequency recurrence, thereby preventing seizures (Gupta & Tripp, 2022).

Relationship of Anticonvulsants as Seizure Prophylaxis in Traumatic Brain Injury Patients

The study conducted by Wang et al. of 11 studies of 2450 patients, comparing various anticonvulsants prophylaxis to prevent early and late PTS in patients with TBI, it was found that Phenytoin can reduce early PTS compared to placebo (Wang et al., 2022). This is in line with Thomson et al., who states that the administration of anticonvulsants (Carbamazepine, Phenobarbital, Phenytoin, Levetiracetam and Valproate) in preventing early PTS showed effective results in TBI when compared to placebo and effectively reduced the occurrence of early PTS after head injury compared to placebo. No statistically significant differences were observed when Phenytoin and anticonvulsants were administered to others (Thompson et al., 2015).

A study conducted by Kumar et al. stated that prophylactic anticonvulsant therapy with Phenytoin for 21 days was no more effective than prophylactic therapy with Phenytoin given for seven days to reduce the frequency of seizures in TBI patients (Kumar et al., 2022). This is similar to Kirmani et al., who revealed that anticonvulsants have proven beneficial in the first seven days after injury, where Phenytoin remains the anticonvulsant of choice because treatment with Phenytoin is effective as a prophylaxis for seizures in TBI patients (Kirmani et al., 2016).

The study conducted by Wat et al. recommends Phenytoin as prophylaxis in early PTS in severe TBI even though early PTS is not associated with a poor prognosis and prophylaxis with anticonvulsant drugs is not recommended as a prevention of late PTS (Wat et al., 2019). This aligns with Torbic et al., who recommended using Phenytoin for early PTS prophylaxis and stated that Valproate had shown similar efficacy to Phenytoin. However, its use may increase mortality (Torbic et al., 2013). The study by Khan et al. stated that the administration of Phenytoin could indicate an early PTS event which had to be given only for the first seven days (Younus et al., 2018).

CONCLUSION

Traumatic Brain Injury is a non-degenerative, non-congenital disorder of the brain that occurs due to external mechanics that can cause permanent or temporary impairment of cognitive, physical and psychosocial functions. One of the complications of TBI is PTS. The use of anticonvulsants with Phenytoin as a recommendation has been shown to prevent the occurrence of PTS in early-onset seizures in patients with TBI.

REFERENCES

- Capizzi, A., Woo, J., & Verduzco-Gutierrez, M. (2020). Traumatic Brain Injury: An Overview of Epidemiology, Pathophysiology, and Medical Management. *Medical Clinics of North America*, 104 (2), 213–238. <https://doi.org/10.1016/J.MCNA.2019.11.001>
- Dawodu, ST (2021). Traumatic Brain Injury (TBI) - Definition, Epidemiology, Pathophysiology: Overview, Epidemiology, Primary Injury. *Physical Medicine and Rehabilitation*.
- Dewan, MC, Rattani, A., Gupta, S., Baticulon, RE, Hung, YC, Punchak, M., Agrawal, A., Adeleye, AO, Shrimel, MG, Rubiano, AM, Rosenfeld, JV, & Park, K.B. (2018). Estimating the global incidence of traumatic brain injury. *Journal of Neurosurgery*, 130 (4), 1080–1097. <https://doi.org/10.3171/2017.10.JNS17352>
- Gupta, M., & Tripp, J. (2022). Phenytoin. *Encyclopedia of Toxicology: Third Edition*, pp. 895–897. <https://doi.org/10.1016/B978-0-12-386454-3.00771-5>
- Ministry of Health. (2018). *RISKERDAS Main Results 2018*. Republic of Indonesia Ministry of Health.
- Kirmani, BF, Robinson, DM, Fonkem, E., Graf, K., & Huang, JH (2016). Role of anticonvulsants in the management of posttraumatic epilepsy. *Frontiers in Neurology*, 7, 32. <https://doi.org/10.3389/FNEUR.2016.00032/BIBTEX>

- Kumar, S., Bharti, A., Prasad, R., Kumari, S., Singh, A., & Yadav, G. (2022). Efficacy of Phenytoin for seven days versus 21 days as a prophylactic anticonvulsant in traumatic brain injury patients - A comparative study. *Journal of Family Medicine and Primary Care*, 11 (8), 4805. https://doi.org/10.4103/JFMPC.JFMPC_486_22
- Lucke-Wold, BP, Nguyen, L., Turner, RC, Logsdon, AF, Chen, YW, Smith, KE, Huber, JD, Matsumoto, R., Rosen, CL, Tucker, ES, & Richter, E. (2015). Traumatic brain injury and epilepsy: Underlying mechanisms leading to seizures. *Seizure*, pp. 33, 13–23. <https://doi.org/10.1016/J.SEIZURE.2015.10.002>
- Mollayeva, T., Mollayeva, S., & Colantonio, A. (2018). Traumatic brain injury: sex, gender and intersecting vulnerabilities. *Nature Reviews Neurology* 2018 14:12, 14 (12), 711–722. <https://doi.org/10.1038/s41582-018-0091-y>
- Mukherjee, S., Arisi, G., Mims, K., Hollingsworth, G., O'Neil, K., & Shapiro, LA (2020). Neuroinflammatory mechanisms of posttraumatic epilepsy. *Journal of Neuroinflammation* 2020 17:1, 17 (1), 1–11. <https://doi.org/10.1186/S12974-020-01854-W>
- National Institute of Neurological Disorders and Stroke. (2023). *Traumatic Brain Injury (TBI)*.
- Thompson, K., Pohlmann-Eden, B., Campbell, LA, & Abel, H. (2015). Pharmacological treatments for preventing epilepsy following traumatic head injury. *The Cochrane Database of Systematic Reviews*, 2015 (8). <https://doi.org/10.1002/14651858.CD009900.PUB2>
- Torbic, H., Forni, A., Anger, K., Degrado, JR, & Greenwood, BC (2013). Use of antiepileptics for seizure prophylaxis after traumatic brain injury. *American Journal of Health-System Pharmacy*, 70 (9), 759–766. <https://doi.org/10.2146/AJHP120203>
- Wang, BC, Chiu, HY, Luh, HT, Lin, CJ, Hsieh, SH, Chen, TJ, Wu, CR, & Chen, PY (2022). Comparative efficacy of prophylactic anticonvulsant drugs following traumatic brain injury: A systematic review and network meta-analysis of randomized controlled trials. *PLoS One*, 17 (3). <https://doi.org/10.1371/JOURNAL.PONE.0265932>
- What, R., Mammi, M., Paredes, J., Haines, J., Alasmari, M., Liew, A., Lu, VM, Arnaut, O., Smith, TR, Gormley, WB, Aglio, LS, Mekary, RA, & Zaidi, H. (2019). The Effectiveness of Antiepileptic Medications as Prophylaxis of Early Seizure in Patients with Traumatic Brain Injury Compared with Placebo or No Treatment: A Systematic Review and Meta-Analysis. *World Neurosurgery*, 122, 433–440. <https://doi.org/10.1016/J.WNEU.2018.11.076>
- Younus, SM, Basar, S., Ahmed Gauri, S., Ahmed Khan, A., Imran, M., Abubakar, S., Sheikh, D., Shehbaz, N., & Ashraf, J. (2018). Comparison of Phenytoin versus Levetiracetam in Early Seizure Prophylaxis after Traumatic Brain Injury, at a Tertiary Care Hospital in Karachi, Pakistan Original Article. *Asian Journal of Neurosurgery*, p. 1096. https://doi.org/10.4103/ajns.AJNS_125_17
- Zimmermann, LL, Diaz-Arrastia, R., & Vespa, PM (2016). Seizures and the Role of Anticonvulsants After Traumatic Brain Injury. *Neurosurgery Clinics of North America*, 27 (4), 499–508. <https://doi.org/10.1016/J.NEC.2016.06.001>



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