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COMPARISON OF SEIZURE-FREE RATES BETWEEN LEVETIRACETAM AND PHENYTOIN ADMINISTRATION IN SEIZURE PATIENTS WITH BRAIN METASTASES TUMOR (BM) DURING PERIOD JANUARY 2023-DECEMBER 2024

Dhiandra Dwi Hapsari*, Teddy Tejomukti, Ranum Anggun Nastiti

***Correspondence:** dio.cassandra.vl@gmail.com*
Department of Neurology, Faculty of Medicine, Universitas Sebelas Maret, Surakarta, Indonesia

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ABSTRACT

Background: Brain metastase tumor (BM) is the most frequently found intracranial tumor. The prevalence of seizures in BM ranges from 30%-50%. One of the treatments for seizure patients with BM is the administration of Anti-Epileptic Drugs (AED). The latest neuropharmacology now makes Levetiracetam (LEV) the first-line choice in BM cases compared to phenytoin (PHT), which was previously often used in BM cases.
Objective: This study aims to compare seizure-free rates in patients with seizures on BM who received PHT or LEV treatment at Regional General Hospital Dr. Moewardi Surakarta from January 2023 – December 2024.
Methods: An observational study using a cross-sectional method with a retrospective approach. Patients included were patients with BM who experienced seizures and received AEDs, either PHT 2x100 mg or LEV 2x500 mg, for a minimum duration of 6 months during the period January 2023–December 2024.
Results: There were 50 research subjects with an age range of 38-67 years. The independent T-Test showed a significance value of 0.007 < value (0.05). In the group of patients given PHT, the seizure-free rate was 6.83±1.26 a (7 months), while in the LEV group, it was 9.02±0.85 b (9 months).
Conclusion: A longer seizure-free rate in research subjects with LEV than PHT was found. This result is to previous research regarding the effectiveness of LEV as the leading choice in seizure patients with BM.

Keywords: anti-epileptic drug, brain metastases, epilepsy, seizure-free

Introduction

Brain metastases (BM) are one of the neurological complications of systemic malignancies. Every year, the incidence of newly diagnosed BM is around 3-10 times higher than primary brain tumors.[1] Approximately 30 to 50 percent of adult patients with brain cancer experience BM. Seizures in BM have a recurring tendency to lead to epileptic conditions. Epilepsy is a brain disorder characterized by a persistent tendency to cause epileptic seizures. Epilepsy is said to be two seizures without provocation or two reflex seizures with a time interval between seizures of more than 24 hours, or one seizure without provocation with the possible risk of recurrent seizures in the next ten years being the same as having two seizures without provocation, or an epileptic syndrome already being established.[2]

Brain metastase tumor patients with uncontrolled seizures can have a negative impact in terms of the social, economic, quality of life, and neurocognitive function of the patient.[3] According to medical record data at Dr. Moewardi Surakarta, 783 BM patients, 384 male adult patients, and 399 female patients seek treatment at Dr. Hospital. Moewardi for January 2023 – December 2024.[4] Anti-epileptic drugs in BM cases

commonly used are divided into first and second generation. First generation is phenytoin (PHT), carbamazepine (CBZ), valproic acid (VPA), ethosuximide, benzodiazepines and barbiturates, while the second generation includes levetiracetam (LEV), gabapentin, lamotrigine, pregabalin, zonisamide, oxcarabazepine, and topiramate.[5] The choice of AED drugs in BM cases must be seen from various principles, including level of efficacy, tolerability, safety, drug interactions, comorbidities, and cost. Phenytoin, as a first-generation AED, is often used as a therapeutic option in BM. Phenytoin works by reducing the entry of Na^+ and Ca^{2+} into nerve cells and encouraging the release of GABA. Currently, in providing seizure prophylaxis therapy in BM cases, 85% of medical personnel use LEV. The use of PHT by most medical personnel, including at the author's hospital site, did not relate to any financing issue. Phenytoin is the traditional use of AED by neurosurgeons, although the transition from PHT use to other AED drugs has occurred.[6-11]

Levetiracetam is a second-generation AED often used in BM patients, which works by binding to synaptic proteins and preventing calcium release. Levetiracetam is almost always given to patients with BM due to brain edema rather than PHT because PHT interacts with corticosteroids. Several studies have proven that the use of LEV as an AED has therapeutic advantages in BM cases.[12] However, research on improvement by LEV is still low because of the use of PHT, historically, as a prophylactic AED for BM. The need for antiepileptic drugs related to patients with BM is essential because of the risk of seizures. Although research shows the risk of seizures in BM patients is 3%, each seizure that occurs will worsen intracranial pressure and cause severe muscular contractions, causing a decrease in patient prognosis. Thus, the selection of epilepsy drugs with the best effectiveness and minimal side effects is needed so as not to worsen the condition of BM.[13] Therefore, this study aimed to compare seizure-free rates in seizure patients with BM who received PHT or LEV treatment at Regional General Hospital Dr. Moewardi Surakarta from January 2023 – December 2024.

Methods

This research is an observational retrospective cross-sectional study. The research subjects were all BM patients diagnosed with seizures and receiving AED treatment, either LEV or PHT, then evaluated from January 2023 – December 2024, who met the inclusion and exclusion criteria. Data was collected through medical records of patients who met the restriction criteria determined by the author. In the medical records, the author processed gender data, age data, tumor location, and the duration of treatment with PHT and LEV. Additionally, the seizure-free period for each treatment was also recorded. This data was carefully analyzed to assess the outcomes of the treatments provided.

Inclusion criteria were 1) all seizure patients with BM, 2) consumption of first generation (PHT) 2x100 mg/day or second generation (LEV) 2x500 mg/day AED monotherapy with a minimum duration of administration of 6 months and assessed for 1 year. Exclusion criteria: 1) Patients with incomplete medical record data, 2) Patients with blood sugar <36 mg/dl or >450 mg/dl; Sodium <115 mg/dl, Calcium <5 mg/dl, Magnesium <0.8 mg/dl, blood urea nitrogen (BUN) >100 mg/dl, and Creatinine >10 mg/dl. The required sample size was calculated using a purposive sampling technique involving 50 research subjects. All data was assessed using SPSS version 27. A data normality test was conducted using the Shapiro-Wilk, followed by a homogeneity test. The independent T-test assessed the comparison of LEV and PHT on seizure-free rates. The data supporting this study's findings are available from the corresponding author upon reasonable request.

Results

The study showed that 52% of the research subjects were men. The average age of the research subjects was 54.6±9.16 and was dominated by the age group 46-65 (Table 1). The location of the primary tumor in both the LEV and PHT groups was dominated by the lungs, followed by the breasts (Figure 1). The average duration of treatment in the PHT group was 7 months, while in the LEV group, it was dominated by 10 months (Figure 2). Shapiro Wilk obtained PHT results of 0.283 and LEV 0.090. Homogeneity Levene Test was 0.093. The independent T-test was obtained <0.05. Mean seizure freedom in seizure patients with BM who received LEV was approximately 9.02 ± 0,85 b (9 months) longer compared to those in the PHT group, 6.83 ± 1.26 (7 months) (Figure 3).

Table 1. Subject Characteristic

Gender	**n**	**%**
Man	26	52
Woman	24	48
Age (54.6±9.16 years old)		
26-45	8	16
46-65	37	74
≥ 66	5	10

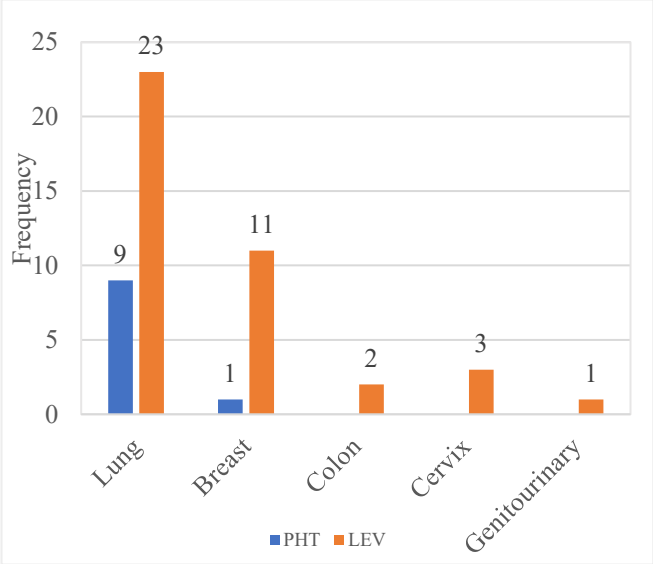

Figure 1. Frequency of primer tumor site

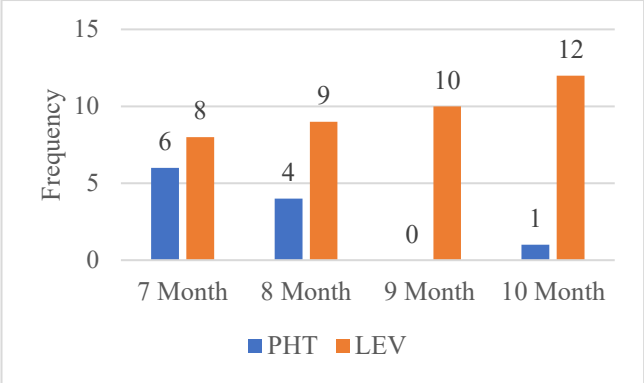

Figure 2. Treatment duration based on group

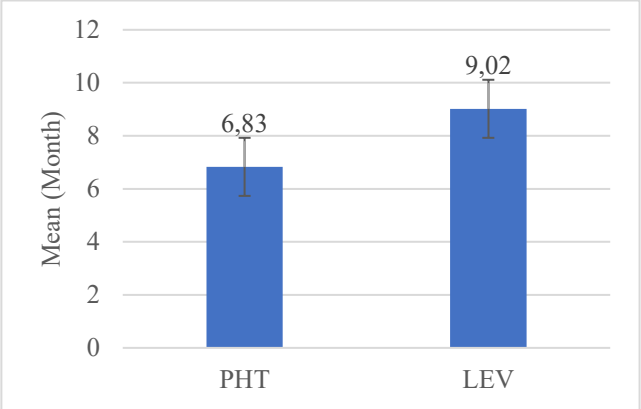

Figure 3. Mean seizure-free period of therapy group

Discussion

The essential age characteristics in this study show an age range of 38 to 67 years. The risk of BM increases at 45 years and over and is highest at ages over 65 years. Research shows that the highest incidence of BM is found at 50-80 years old.[12] Another study shows the peak incidence is in the age group > 65.[14]. Most BM patients in this study were 37 people aged 46 to 65. Research by Nasution *et al*. states respondents with BM were found to have a mean of 51.74±11.17 years of age.[15] Increasing risk of BM with increasing age is due to the pathophysiology of BM, which is a multifaceted and complex process.

The proteolytic activity of the extracellular matrix will accelerate cell proliferation and angiogenesis. This causes an electrochemical imbalance, which increases the number of neurotransmitters that inhibit cell function and cause cell death. The complex process in cases of brain metastases is called the metastatic cascade. Cancer cells are released when the primary tumor invades surrounding healthy tissue, which is then carried by the bloodstream, trapped, and carried along during the extravasation of plasma, which is the end artery. Later, if the cancer cells can survive, the cells will experience proliferation, and a metastasis process will occur.[14] Other things that influence this are also caused by environmental exposure and lifestyle in BM patients.[16]

In this study, the female and male populations were 48% and 52%, respectively. Studies from Saha et al. stated that brain metastases occur more often in men (52.78%).16 Research conducted by Chao *et al*. (2006), Arierieta *et al.* (2009), and Tao Sun *et al*. (2012) also stated that BM occurs more often in men than in women.[18] Another study shows that the risk of men experiencing BM is higher than women (1.60 vs 1.52). The incidence of BM is more common in adults (15-20%) than in the pediatric group (5-10%).[14]

The incidence of BM reaches 9-17%, with the most common BM from originate site being 67-80%, originating from the lung (80%), breast (3.7%), and melanoma (3.8%), with a mortality rate reaching 10-26%. Research conducted by Jill *et al*. (2004) stated that in BM cases, most initial tumor sites were lung, 19.9%; melanoma, 6.9%; kidney, 6.5%; breast, 5.1%; and colorectal, 1.8%.[14] Research from Neurona (2020) also stated that in adult patients, the primary tumors that most often metastasize to the brain originate in the lungs (36%-64%), breast (15%-20%), and melanoma (5%-20%).[19] Metastasis to the brain parenchyma involves involvement of the Central Nervous System (CNS) with hematogenous spread. Tumor cells from the lungs will follow the left heart circulation. Cardiac output to the brain is approximately 20%, causing metastases from the lungs that tend to the brain. Brain metastases tumor tends to occur in the gray-white matter junction area, which experiences extravasation across the blood-brain barrier (BBB), enters the brain parenchyma, and the angiogenesis process occurs.[20]

Brain metastases tumor contributes to 6-10% of the incidence of epilepsy. The incidence of seizures is around 65-75% in glioma patients due to grade 2 isocitrate dehydrogenase (IDH) mutations, 25-60% in high-grade glioma patients, 25-30% in grade 4 IDH, 30-50% in meningioma patients, and reaches 20-35%

of patients with BM. Another systematic review showed that of a total of 660 patients with seizures due to BM, the incidence was most often caused by glioma, meningioma, and metastasis.[21]

It was stated in this study that the efficacy of monotherapy in BM cases was 6 months in PHT, while in LEV, it was 12 months.[20] Etiopathogenesis of seizures in BM is multifactorial, including regional ischemia, which causes compression due to tumor enlargement, metabolic changes such as acidosis, blood-brain barrier disorders due to leakage fluid or protein, hypoxia, glial inflammation, and tissue damage. Various other regional changes related to tumor cells, interactions with neurons, inflammatory processes, molecular factors, receptor activity, and neurotransmitter imbalances coexist with these mechanical changes.[16]

To the author's knowledge, no study has been published on the duration of AED administration on seizure-free duration. Thus, The Korean Society for Neuro-Oncology (KSNO) states that for patients who have never had seizures and without postoperative seizures, it is recommended to stop or reduce AED(s) 1 week after surgery. In patients who have never had seizures with one early postoperative seizure (<1 week after surgery), it is recommended to maintain AED(s) for at least 3 months before tapering. In patients who have never had seizures with ≥2 postoperative seizures or in patients with a history of preoperative seizures, it is recommended to maintain AEDs for more than 1 year.[22]

The presence of seizures in the peri/postoperative period is the most critical factor in determining the duration of AED prophylaxis. The study by Kim et al. (2020) in patients with BM showed the duration of AED prophylaxis use in 3 groups in sequence, namely group 1 (without a history of seizures before and after surgery), group 2 (without a history of seizures before surgery but a history of seizures after surgery), and group 3 (with a history of seizures before surgery) showed the duration of AED prophylaxis use in group 1 was dominated by 1-3 months (35.7%), in group 2 it was dominated by 6 months-2 years (54.8%), and in group 3 it was dominated by 6-2 years (40.5%).[23] Another study showed that 26% of glioma patients who were seizure-free ≥1 year since the last antitumor treatment experienced recurrent seizures after discontinuing AEDs compared to 8% of patients who continued AED treatment (±2 years).[24]

Studies showed PHT had higher drug side effects due to interactions with CYP450 and the many drug interactions between PHT and other drugs. The mechanism of action of PHT is by reducing excessive excitation in the brain center, which causes epilepsy, and suppressing neuronal hyperexcitability caused by sodium efflux. Meanwhile, LEV's mechanism of action prevents seizures by modifying neurotransmitter release by binding to synaptic vesicle glycoprotein 2A (SV2A). LEV inhibits the effects of Zn^{2+} and β-carboline, which are GABA regulators, and inhibits Ca^{2+} and K^{+}. LEV works well with various anti-epileptic drugs.[17] Guidelines from the International League against Epilepsy (ILEA), Society for Neuro-Oncology (SNO), and European Association of Neuro-Oncology (EANO) recommend BM management of epilepsy cases to avoid the use of 1st generation AEDs and recommend 2nd.[16] Research by Wani *et al*., Noureen *et al*., and Besli *et al*. described the superiority of LEV compared to PHT in status epilepticus in children.[18,19,20] Singh *et al*. reported LEV achieved a therapeutic effect of 100% after 1 hour and 98% after 24 hours, which was superior to phenytoin, amounting to 76% at 4 and 24 hours.[18,21] Appleton *et al*. showed LEV having a 70% reduction in seizure activity compared to PHT with a 64%.[18,25] Levetiracetam was more effective as a transition from IV to oral and did not cause hypotension.[18,26]

The LEV vs. PHT comparative research conducted by Kern et al. in post-craniotomy due to brain tumors showed an incidence (%) of seizures in the LEV vs. PHT group of 2.5 vs. 4.5 ($p>0.05$).[27,28] Iuchi *et al*. in post-craniotomy, incidence (%) of seizures in LEV vs PHT group was 1.4 vs 15.1 ($p<0.05$). Iuchi *et al*. explained the high incidence of seizures in the PHT group due to liver dysfunction (n=1), cutaneous eruptions (n=2), and atrial fibrillation (n=2).[28,29] LEV correlated with a decreased rate of epilepsy and better side effects than PHT. Systematic review shows efficacy of LEV in brain tumor patients with complete response reached 94% in the postoperative period and 84% for long-term use.[28,30]

Fuller *et al*. state PHT had more significant side effects (4/38, $p = 0.08$) than LEV (1/36, $p = 0.09$).[31] Effectiveness of LEV in patients with a mean age of 55.1 years was found to be 54% of LEV as an additional AED and 46% as monotherapy with a mean dose of 1000 mg/day showed LEV group as an additional AED. The frequency of seizures was reduced to 0 per week, while the total seizure frequency of study subjects was reduced by 50% ($p = 0.0002$).[32] Another study shows side effect (%) LEV vs. PHT on glioma patients was six vs. 20, followed by recurrent seizures (%) in 36 of PHT, while the LEV group was ten.[33]

Previous research has explained that LEV's superiority is related to the low number of side effects, especially acute hypotension. Research subjects with PHT administration tended to experience acute hypotension and higher use of vasopressors, which affected cerebral hypoperfusion and worsened the condition of epilepsy. PHT is capable of triggering cardiac arrhythmias. Advantages of LEV include

100% bioavailability, in contrast to PHT, which requires dose evaluation. LEV is easier and faster to administer than PHT, which is time-consuming. [18]

The use of LEV and steroids needs to be investigated further. Corticosteroids are recommended to provide temporary symptomatic relief of symptoms related to increased intracranial pressure and edema secondary to brain metastases. A study by Kim *et al*. in patients with BM showed that 90.5% of respondents used steroids in the perioperative period, including 34.2% of them in a routine manner. The presence of peritumoral edema (90.9%) was considered the most critical factor determining steroid usage, followed by a degree of clinical symptoms (60.6%). The study showed no significant interaction between steroid use and levetiracetam.[23] Thus, steroids and levetiracetam both showed worsening psychological conditions. The study showed anxiety, aggression, paranoia, and severe hostility post-levetiracetam administration. On the one hand, steroid use can induce hypomania, mania, depression, and psychosis, as do cognitive changes, particularly deficits in verbal or declarative memory.[34,35]

The limitation of this study is that we did not assess patient compliance with the duration of treatment or the average duration of seizure-free periods. For further research, it is expected to conduct research with a more significant number of respondents, conduct research with subjects not limited to BM patient seizures, yet only patients with tumors without metastasis, evaluate treatment compliance, and evaluate treatment outside of the drug interventions consumed by patients.

Conclusion

LEV works well and is more effective than PHT, with fewer side effects. Research subjects who received AED monotherapy with LEV had a seizure-free rate of 9.02±0.85 b (9 months), while those with PHT had a seizure-free rate of 6.83±1.26 a (7 months).

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