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Original Article

Perioperative perampanel administration for early seizure prophylaxis in brain tumor patients

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ABSTRACT

Background: The efficacy of perioperative prophylactic antiepileptic drug therapy in "seizure-naïve" patients with brain tumor, including glioblastoma (GBM), remains controversial. This study investigated whether perampanel (PER) is effective and safe for preventing perioperative onset of epileptic seizures, so-called early seizure, in patients with brain tumors.

Methods: Forty-five patients underwent tumor resection through craniotomy for a primary supratentorial brain tumor at Ehime University Hospital between April 2021 and July 2022. PER was administered from the 1st to the 6th day after surgery for seizure prophylaxis. Occurrence of early seizure, hematological toxicities, and various side effects were recorded on postoperative days 7 and 14. In addition, the clinical course of these patients was compared with 42 brain tumor patients under the same treatment protocol who received levetiracetam (LEV) for seizure prophylaxis between April 2017 and October 2018.

Results: In 45 patients with brain tumor, including GBM, who received PER administration, no early seizures were identified within 7 days postoperatively. No adverse drug reactions such as hematological toxicity, liver or kidney dysfunction, or exanthematous drug eruption were observed in any cases. As side effects, somnolence was reported in 14 patients (31.1%), vertigo in 3 patients (6.7%), and headache in 3 patients (6.7%). Although somnolence and vertigo were difficult to assess in the case of intraparenchymal tumors, particularly GBM, these side effects were not identified in patients with extraparenchymal tumors such as meningiomas, epidermoid cysts, and pituitary adenomas. In addition, no significant differences were identified compared to patients who received LEV.

Conclusion: The efficacy and safety of PER in preventing early seizures among patients with brain tumors were retrospectively evaluated. Perioperative administration of PER to patients with brain tumors may reduce the risk of early seizures without incurring serious side effects, showing no significant differences compared to patients who received LEV.

Keywords: Brain tumor-related epilepsy, Early seizure, Glioblastoma, Perampanel, Side effect

INTRODUCTION

Perioperative prophylactic administration of antiepileptic drugs (AEDs) to patients without a history of seizures undergoing brain tumor resection is not recommended due to a lack of

evidence but has been done routinely in many centers.[4,15] Relatively few recent studies have comprehensively examined the actual status of epilepsy treatment in brain tumor patients at multiple institutions. In particular, the efficacy of administering prophylactic AEDs in patients with no history of seizures, so-called "seizure-naïve brain tumor patients," remains controversial.[12,28] In previous reports, the incidence of perioperative seizures among such patients has typically been reported as 5–10%.[6,12,22] Perioperative seizures after craniotomy are associated with longer hospital stays, decreased quality of life (QOL), shorter overall survival, and increased risk of conversion to refractory epilepsy.[5,12] For perioperative prophylactic administration of AEDs to patients with brain tumors, the current preferred drug is levetiracetam (LEV), which is considered superior to older AEDs in terms of pharmacokinetics, tolerability, safety, and interaction profile, as well as considering potential synergistic effects on oncological treatment.[3,12,14,28] Side effects of LEV are generally infrequent and mild but are difficult to use because psychiatric symptoms predominate, particularly in the form of somnolence, asthenia, mood disorders, and behavioral disturbances in patients with brain tumors.[12,23,28] In addition, LEV is poorly permeable to blood-brain barrier (BBB) due to its low lipophilicity, making it difficult for perioperative prophylactic usage.[18]

Perampanel (PER) is a non-competitive α-amino-3-hydroxyl-5-methyl-4-isoxazolepropionate (AMPA) receptor antagonist that is clinically used for seizure control. In preclinical studies, PER has been found to be effective in preventing seizures, and this agent is expected to be particularly useful in controlling epileptic seizures associated with brain tumors, that is, brain tumor-related epilepsy (BTRE).[11,13,17,25] Furthermore, PER has good BBB permeability and has been reported to keep its concentrations in the brain after transferring from plasma.[8] Based on these findings, we hypothesized that PER may be appropriate as a perioperative agent in the neurosurgical setting. Therefore, this study aims to investigate the short-term effects of perioperatively administered PER for brain tumor patients, particularly those with malignant glioma, not only in terms of the effectiveness of seizure control but also in terms of side effects and hematotoxicity.

MATERIALS AND METHODS

This study was approved by the Ethics Committee for Clinical Research at Ehime University Hospital (approval no. 2110012). All procedures were performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained from all individual participants included in the study.

Patients and study design

This study retrospectively enrolled 87 patients with brain tumor planned with inpatient treatment including surgical resection in the Department of Neurosurgery at Ehime University Hospital between April 2017 and August 2022. Among these patients, all 45 patients treated by Akihiro Inoue (Inoue. A) from April 2021 to August 2022 were administered PER perioperatively, while all 42 patients treated by Inoue A from April 2017 to October 2018 received LEV. Informed consent was obtained from all individual participants enrolled in the study. Specifically, participants were informed regarding the risk of the surgical procedure and the potential risks of microsurgery and chemoradiotherapy. This study included seizure-naïve adult (>18 years old) patients presenting with a radiologically suspected primary supratentorial brain tumor and all underwent craniotomy for tumor resection obtaining a histopathological diagnosis. Exclusion criteria comprised contraindications for PER or LEV (according to the relevant time period), and pre-existing administration of anticonvulsive medications. The total study duration for each patient was 15 days. The study design is shown in Figure 1.

PER and LEV administration, and assessment of early seizure

All enrolled patients with supratentorial brain tumor were administered oral PER or LEV during the perioperative period for a total of 6 days after surgery. In addition, all patients did not receive any preoperative AEDs including PER and LEV. The dose was 2.0 mg/day for PER and 1000 mg/day for LEV. All patients were hospitalized at Ehime University Hospital for ≥14 days after surgery and were evaluated for the occurrence of early seizures during the hospitalization period. In this study, early seizure was defined as epilepsy occurring within 1 week after surgery. If early seizures were suspected clinically, electroencephalography was performed. In addition, in cases with intraparenchymal tumors, cognitive function was assessed by mini-mental state examination (MMSE) preoperatively and postoperative day 14.

Evaluation of hematological toxicity and various side effects

Hematological laboratory markers including neutrophils, platelets, hemoglobin, lymphocytes (total), and presence of febrile neutropenia were evaluated on postoperative days 7 and 14 for all enrolled patients. Self-reported side effects were also elicited during hospitalization. All patients underwent routine magnetic resonance imaging (MRI) at least once within 5 days postoperatively to rule out postoperative complications such as bleeding or ischemia and to depict the amount of resection.

Statistical analysis

Values are expressed as the mean ± standard deviation, and data were compared using the two-tailed Student's

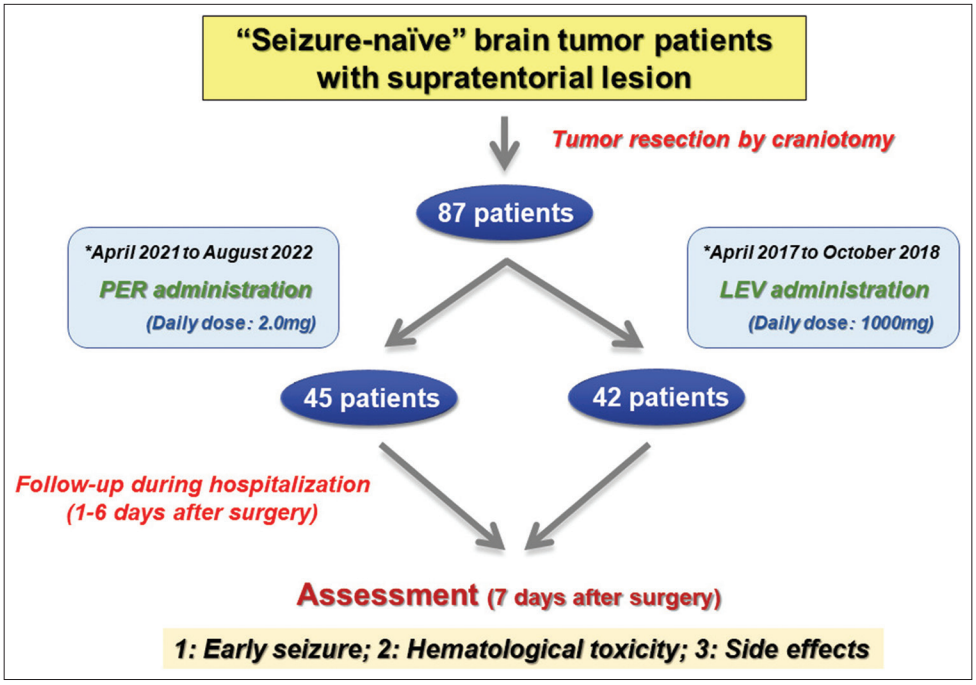

Figure 1: Study flow chart. During the study period, 87 "seizure-naïve" brain tumor patients were included in this study. Of these, 45 patients cured between April 2021 and August 2022 were administered perampanel during the perioperative period, ranging from 1 to 6 days after surgery, and 42 patients cured between April 2017 and October 2018 were administered levetiracetam during the same period for early seizure prophylaxis. At 7 days after surgery, we assessed the occurrence of early seizure and evaluated hematotoxicities and various side effects. PER: perampanel, LEV: levetiracetam.

t-test (unpaired) and the chi-square test. Significance was set for values of $P < 0.05$. All analyses were performed using Office Excel 2016 software (Microsoft, Redmond, WA, USA).

RESULTS

Patient characteristics

Among the 87 patients with intracranial brain tumor enrolled at our institution during the study period, 45 subjects prophylactically received PER, and 42 received LEV during the perioperative period. All seizure-naïve patients with supratentorial brain tumor for whom MRI could be performed were enrolled in this study. All patients underwent the same protocol of microsurgical resection by echo-linked navigation-guided microsurgery using MRI and methionine-positron emission tomography fusion images and fence-post catheter technique. [19] Postoperative MRI was performed 1–3 days after surgery for patients with intraparenchymal tumors, and 1–5 days for the other tumors. In the PER group, the mean age of the 45 patients (23 men, 22 women) was 64.3 years (range, 37–88 years). Subjects presented a median Karnofsky performance status (KPS) score of 80 (range, 50–100). Histopathological evaluations were verified by the World Health Organization classification system 2021. Of these 45 patients, glioblastoma (GBM) was confirmed in 18 patients, diffuse large B-cell lymphoma (DLBCL) in eight patients, adenocarcinoma (metastatic tumor) in six patients, meningioma in eight patients, pituitary adenoma in two patients, epidermoid cyst in two patients, and hemangioblastoma in one patient. In the LEV group, the mean age for the 42 patients (23 men and 19 women) was 62.9 years (range, 40–85 years) with a median KPS score of 80 (range, 50–100). The histopathological evaluation confirmed GBM in 17 patients, anaplastic oligodendroglioma in one patient, ependymoma in one patient, DLBCL in five patients, adenocarcinoma (metastatic tumor) in seven patients, meningioma in nine patients, solitary fibrous tumor in one patient, and epidermoid cyst in one patient. In both groups, tumors in GBM patients lacked mutation in the gene encoding isocitrate dehydrogenase-1 (*IDH-1*) as analyzed by Sanger sequencing.[21] With regard to the resection rate, except for malignant glioma and DLBCLs, all other tumors were resected both grossly and radiographically. For DLBCLs, surgery was limited to biopsy. On the other hand, with regard to malignant glioma, the extent of resection was evaluated by volumetric analysis on MRI before and after surgery, as described previously.[20] In the PER group, gross total resection (GTR; 100% resection of tumor volume) was achieved in 30 patients (66.7%), subtotal resection (STR; 95– < 100% resection) in 1 patient (2.2%), partial resection (PR; 60– < 95% resection) in 4 patients (8.9%), and biopsy

(<60% resection) in 10 patients (22.2%). In the LEV group, GTR was achieved in 28 patients (66.7%), STR in 2 patients (4.8%), PR in 5 patients (11.9%), and biopsy in 7 patients (16.7%). All patients with GTR of malignant glioma received extensive resection of the infiltrating part of tumor in the non-contrast-enhanced area around the gadolinium-enhanced tumor mass with the aid of fluorescence guidance using 5-aminolevulinic acid (extensive total resection). No significant differences were identified between patients who received PER and LEV administration ($P > 0.05$). Patient characteristics are summarized in Table 1.

Occurrence of early seizure and adverse events (AEs)

In this study, all 87 patients underwent craniotomy performed by the same surgeon (Inoue. A) under the same protocol using image-guided navigation. Computed tomography was performed immediately after surgery and the day after surgery, and MRI was performed within 10 days of craniotomy, with no obvious postoperative hemorrhage or extensive ischemic infarction observed. In addition, no severe infections, unexpected postoperative complications, or postoperative psychotic symptoms that would have caused a decrease in KPS were identified. In terms of epileptic events, early seizures were not recognized in any of the 87 brain tumor patients during the 14-day observation period [Table 2]. All patients were able to complete PER or LEV administration 6 days after surgery, as scheduled. In addition, cognitive function was assessed by MMSE only in cases with intraparenchymal tumors, with the score of 25.0 and 25.0, pre- and postoperatively in PER group, which was 26.0 and 26.0 in LEV group. There were no significant differences between the preoperative and postoperative periods for both groups ($P > 0.05$).

Analysis of hematological toxicity

To determine hematotoxicities associated with PER or LEV administration, we used the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE ver. 5.0) classification of hematotoxic AEs. We assessed laboratory examinations at two points on postoperative days 7 and 14 in line with CTCAE ver. 5.0 criteria. According to this classification, no hematological AEs were categorized as Grade 4 or reported as related to PER or LEV administration in any of the patients in this study. In addition, no hematotoxicities classified as Grade 1–3 were observed in patients during this follow-up period. No hepatic or renal dysfunction was recognized in any cases either [Table 2].

Assessment of various side effects

A precise frequencies of each side effects and their severities over the entire study period can be found below. In the PER group, somnolence was the most frequent AE, as reported in 14 patients (31.1%). Vertigo was reported in 3 patients (6.7%) and headache in 3 patients (6.7%). In the LEV group, somnolence was seen in 13 patients (31.0%), vertigo in 3 patients (7.1%), and headache in 5 patients (11.9%). However, across the two groups, no patients reported other side effects, such as tremor, lightheadedness, and exanthematous drug eruption. While somnolence and lightheadedness were difficult to assess in cases of intraparenchymal tumors such as malignant glioma, these side effects were not identified in extraparenchymal tumor patients such as those with meningioma, pituitary adenoma, epidermoid, or hemangioblastoma.

DISCUSSION

Epileptic seizures associated with brain tumors, so-called BTRE, can cause motor and cognitive impairments such as Todd's palsy that can significantly impair patient QOL. The incidence of BTRE is as high as 40–60%, often representing the first clinical manifestation of tumor, and providing a sign of progression or recurrence.[27] The control of BTRE is thus very important in the treatment of brain tumors. On the other hand, early seizures that occur after brain tumor resection may be due to traumatic changes associated with surgery and may need to be considered as a separate condition from BTRE. Although practical guidelines published by the American Academy of Neurology in 2000 do not recommend the use of AEDs,[7] most neurosurgeons administer AEDs for perioperative seizure prevention.[4] In particular, early seizures in the perioperative period, occurring less than 7 days after brain tumor resection by craniotomy, require attention due to the risk; it has of interfering with subsequent treatment.

Although the efficacy of AEDs in preventing early seizure remains controversial, we have administered AEDs postoperatively in all patients unless a history of adverse effects was present. These seizures are classified as early posttraumatic seizure (PTS) caused by the surgical procedure. We, therefore, speculated that the choice of AEDs for prophylaxis of postoperative early seizure may be appropriate for treatment similar to the prophylaxis of early PTS. The guidelines for severe traumatic brain injury based on the Brain Trauma Foundation recommend prophylactic administration of phenytoin,[1] which is widely used in epilepsy treatment. On the other hand, LEV, a novel AED widely used in seizure control, has been reported as unequivocally effective for preventing early PTS.[9] LEV has few serious side effects and does not require monitoring of drug levels in the plasma, representing advantages for preventing early PTS. However, Brain Trauma Foundation guidelines do not recommend preoperative administration of LEV. In addition, LEV can cause psychiatric symptoms as a side effect and has low BBB permeability due to low lipophilicity,[18] making it difficult to use for controlling

Table 1: Characteristics of patients enrolled in this study.

Parameter	Value		
	PER group	LEV group	p
No. of patients	45	42	-
Female sex (%)	22 (48.9)	19 (45.2)	1
Age (years), median (range)	64.3 (37-88)	62.9 (40-85)	0.8126
Type of pathology (%)			
Glioblastoma, IDH wild type)	18 (40.0)	17 (40.5)	0.7584
Oligodendroglioma, IDH mutant, 1p/19q-codeleted	0 (0)	1 (2.4)	0.3118
Supratentoirial ependymoma	0 (0)	1 (2.4)	0.3118
Diffuse large B-cell lymphoma	8 (17.8)	5 (11.9)	0.2384
Adenocarcinoma	6 (13.3)	7 (16.7)	0.6592
Meningioma	8 (17.8)	9 (21.4)	0.6943
Solitary fibrous tumor	0 (0)	1 (2.4)	0.3118
Epidermoid cyst	2 (4.4)	1 (2.4)	0.4687
Pituitary adenoma	2 (4.4)	0 (0)	0.1473
Hemangioblastoma	1 (2.2)	0 (0)	0.3061
Surgical procedure (%)			
Craniotomy	45 (100)	42 (100)	1
Degree of resection (%)			
Gross total resection	30 (66.7)	28 (66.7)	0.4945
Subtotal resection	1 (2.2)	2 (4.8)	0.3115
Partial resection	4 (8.9)	5 (11.9)	0.5991
Biopsy	10 (22.2)	7 (16.7)	0.2771

"Value" represents the number of patients unless otherwise noted.
PER, perampanel
LEV, levetiracetam
IDH, isocitrate dehydrogenase

Table 2: Outcomes about early seizure, hematologic toxicity, and side effects.

Parameter	Value			
	Total	PER group	LEV group	p
No. of patients	87	45	42	-
Postoperative complication, n (%)	0	0 (0)	0 (0)	-
Early seizure, n (%)	0	0 (0)	0 (0)	-
Hematologic toxicity (CTCAE ver. 5.0), n (%)				
Grade 1-3	0	0 (0)	0 (0)	-
> Grade 4	0	0 (0)	0 (0)	-
Side effects, n (%)				
somnolencesomnolence	27	14 (31.1)	13 (31.0)	0.422
vertigo	6	3 (6.7)	3 (7.1)	0.398
headache	8	3 (6.7)	5 (11.9)	0.799
others (tremor, lightheadedness, drug eruption e.t.c)	0	0 (0)	0 (0)	-

"Value" represents the number of patients unless otherwise noted.
No, number
n, number
PER, perampanel
LEV, levetiracetam
CTCAE, common terminology criteria for adverse events

early seizure in the perioperative period after brain tumor resection. The Tmax to plasma of LEV is reported as 0.4–0.7 h, which is 2.0–2.5 h in the central nervous system, suggesting a delay from brain transit.[26]

Recently, glutamate has been featured as a key excitatory neurotransmitter in the brain, and excessive glutamate release and receptor overactivation are thought to be involved in the neurological damage caused by traumatic

brain injury.[2,16] These reports suggest that the cause of early seizure may be extrinsic brain damage associated with surgery and that controlling glutamate may prevent early postoperative seizure following brain tumor resection. We, therefore, focused on PER, one of the newer AEDs. PER is a novel AMPA receptor antagonist approved as an adjunctive therapy for the treatment of seizures with infrequent side effects.[11] Some experimental data indicate that PER could exert neuroprotective effects in various neurological disorders, including intracranial hemorrhage, ischemic stroke, and traumatic injury.[2] Yu *et al*. reported that PER showed protective effects against brain damage following traumatic brain injury in rats via both anti-oxidative and anti-inflammatory activity.[29] In addition, Hibi *et al*. reported that the ratios of brain to plasma concentrations after PER administration were 1.06 (data in mice, 60 min after administration) and 1.14 (rats, 30 min), indicating its good BBB permeability and excellent transfer to the brain.[8] Furthermore, PER is known to inhibit epilepsy as well as glioma progression.[10,24] Ishiuchi *et al*. reported that AMPA-type glutamate receptors are expressed in GBM and their activation leads to phosphorylation of Akt, a key signaling molecule maintaining the malignant phenotype of glioma. It has also been shown that inhibition of AMPA-type receptor suppressed the growth and invasion of glioma cells.[10] Taking these factors into consideration, the use of PER for the prevention of early seizure after brain tumor resection could theoretically represent a powerful therapeutic option for treating malignant gliomas as well as general brain tumors. However, PER is currently only available in an oral formulation, making this agent difficult to use in patients with impaired consciousness in the early postoperative period. The development of intravenous formulations is, thus, expected.

We only have small preliminary data of our own on blood concentrations; however, they reach the optimal range (50–400 ng/mL) within 3 days after administration of PER (2.0 mg/day) (unpublished data). In the present study, no cases of early seizure were identified in the PER group up to postoperative day 7, even in patients with intra-axial tumors such as malignant glioma and malignant lymphoma. In addition, no serious hematotoxicities more than Grade 2 of CTCAE ver. 5.0 were seen, and also, no cognitive decline has been observed. However, a small number of side effects such as somnolence, headache, and dizziness appeared. As in the PER group, the LEV group showed no occurrence of early seizure and no significant AEs in the form of hematotoxicities. However, as in the PER group, side effects such as somnolence, headache, and dizziness were identified. As a result, no significant differences were apparent between PER and LEV groups in terms of side effects ($P > 0.05$). The present cohort showed no significant differences in age, sex, KPS score, pathological findings, or *IDH-1* mutational status (as assessed by Sanger sequencing) between the groups. We likewise detected no significant differences in the extent of resection between GTR and non-GTR groups (i.e., STR, PR, or biopsy). Taken together, perioperative administration of PER to "seizure-naïve" brain tumor patients may reduce the risk of early seizures without serious side effects, showing no significant differences compared to patients who received LEV. This, in turn, may lead to favorable QOL and smooth introduction of chemotherapy and other treatments.

Several limitations to the present study must be kept in mind. This study was conducted by analyzing data from a relatively small number of patients, which may reflect the difficulty of enrolling sufficient numbers of patients with brain tumor-administered PER, a novel AED, perioperatively from only a single center. A control group (no administration of AED) was unavailable, as our institution routinely applied perioperative AEDs for tumor resection. A more extensive analysis with a larger number of patients is needed to obtain definitive conclusions before the proposed modality can be considered truly useful in clinical practice.

CONCLUSION

Perioperative administration of PER to "seizure-naïve" patients with brain tumor, particularly malignant glioma, may reduce the risk of perioperative early seizures without serious hematotoxicities or side effects, showing no significant differences in terms of the effectiveness of seizure control and safety compared to LEV. Also considering its good BBB permeability of PER, these findings may represent a new therapeutic strategy not only for brain tumor treatment but also for every other craniotomy in the field of neurosurgery. This may also lead to better therapeutic planning and an improved clinical course for patients with brain tumor, including malignant glioma.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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