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The First Case of a Single-Dose, Intravenous Perampanel Administration for Early Postoperative Seizure Prophylaxis

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ABSTRACT

Early postoperative epileptic seizure (EPS) may occur in neurosurgical patients. Perampanel has an extended serum half-life plus a rapid onset of action. The intravenous form of perampanel was first launched in Japan, and it may be an option for EPS prevention in brain surgery.

1 | Introduction

Postoperative epileptic seizures may occur in neurosurgical patients, especially when the cerebrum is manipulated. Most previous studies defined "early" postoperative seizure (EPS) as seizures occurring within 7 days after surgery, and the frequency of EPS after brain tumor surgery is estimated to be up to 37.1%, but generally considered to be around 10% [1–14]. Although there is no high-quality evidence or settled opinion on the benefits and drawbacks of prophylactic administration of antiseizure medication (ASM) for postoperative seizure control, ASM is commonly given for a short period of time after surgery in Japan.

Perampanel hydrate (PER) is the only ASM that acts on α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) type glutamate receptors, which are excitatory receptors that exist mainly in the postsynaptic membrane [15]. It exerts antiepileptic effects by selectively and non-competitively antagonizing AMPA receptors, thereby suppressing neuronal excitation. The oral form of PER has been available for several years and is now widely used; an intravenous formulation was found to be equivalent in safety and tolerability to the oral form and was launched in April 2024 in Japan [16], ahead of the rest of the world. This new form expanded the options for intra/postoperative administration of PER for prophylaxis, but there are no current reports on its use for EPS prevention.

Here, we report a world-first case of single-dose, intravenous PER used to prevent EPS. The prophylactic use of PER was approved by the Tsukuba University Clinical Research Review Board (approval number: TCRB23-026) and written, informed consent was obtained.

2 | Case History

An 83-year-old woman with mild dementia but independent indoor living presented with headache, aphasia, and right hemiparesis. Head magnetic resonance imaging (MRI) showed a ring-shaped contrast lesion extending from the anterior half of the left insular cortex to the basal ganglia

Abbreviations: AMPA, α-amino-3-hydroxy-5-Methyl-4-isoxazolepropionic acid; ASM, anti-seizure medication; EPS, early postoperative seizure; MRI, magnetic resonance imaging; PER, perampanel hydrate.

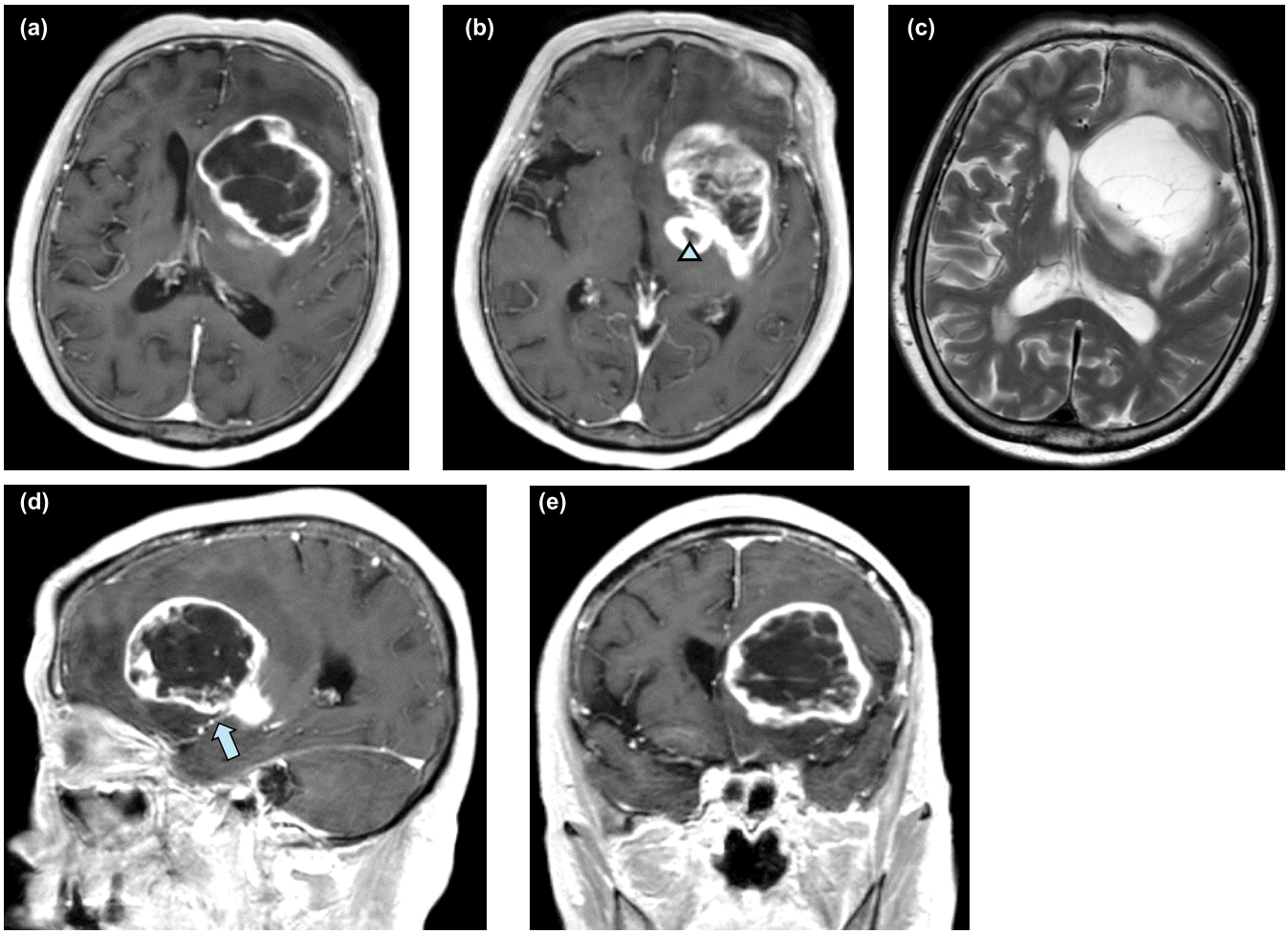

FIGURE 1 | Preoperative MRI. Preoperative brain MRI, revealing a large cystic lesion mainly in the left insular cortex on T2WI (c). The lesion shows a ring-shaped enhancement on axial (a and b), sagittal (d), and coronal (e) post-enhanced T1WIs. It extends to the basal ganglia (arrowhead) and involves perforating arteries, such as the lenticulostriate artery (arrow). MRI, magnetic resonance imaging; WI, weighted image.

(Figure 1). We suspected glioblastoma and decided to perform a partial removal, considering her age and the risk of radical resection. She had no history of epileptic or convulsive seizures, so we did not administer any prophylactic ASM preoperatively.

3 | Treatment

The majority of the tumor was cystic and we performed partial removal of the upper anterior portion of the tumor after opening the cystic window via the middle frontal gyrus (Figure 2). We administered 6 mg of PER dissolved in 100 mL of normal saline intravenously over 60 min during the surgery under general anesthesia and the administration was completed 2.5 h prior to anesthesia awakening (Figure 3). Awakening from general anesthesia was uneventful, with no drug-related adverse events, abnormal laboratory values, or dizziness. Although we did not administer additional ASMs, the patient remained free from EPS. The final pathological diagnosis was glioblastoma, IDH-wildtype, CNS WHO grade 4, and the patient underwent radiation therapy (60 Gy/30 fractions) and chemotherapy with temozolomide.

4 | Outcome and Follow-Up

Although aphasia due to the primary disease remained, hemiparesis improved, and the patient was discharged home after chemoradiation therapy with a Karnofsky performance status of 60. At 6 months postoperatively, there has been no recurrence, and she is living at home with the support of her family.

5 | Discussion

We experienced a world-first case of prophylactic intravenous PER administration under general anesthesia, with persistent freedom from EPS and uneventful surgical recovery. PER has a very long serum half-life of 4 to 5 days (according to the package insert), plus a high permeability across the blood–brain barrier and rapid onset of action [17]. Hence, it is expected to have immediate and long-lasting effects even when administered as a single dose. In addition, since gliomas are considered to induce tumor growth and brain tumor-related epilepsy via AMPA receptor signaling [18, 19], PER, an AMPA receptor antagonist, may be a promising defense. In light of its characteristics, PER is an ideal ASM, especially for preventing EPS in brain tumor patients.

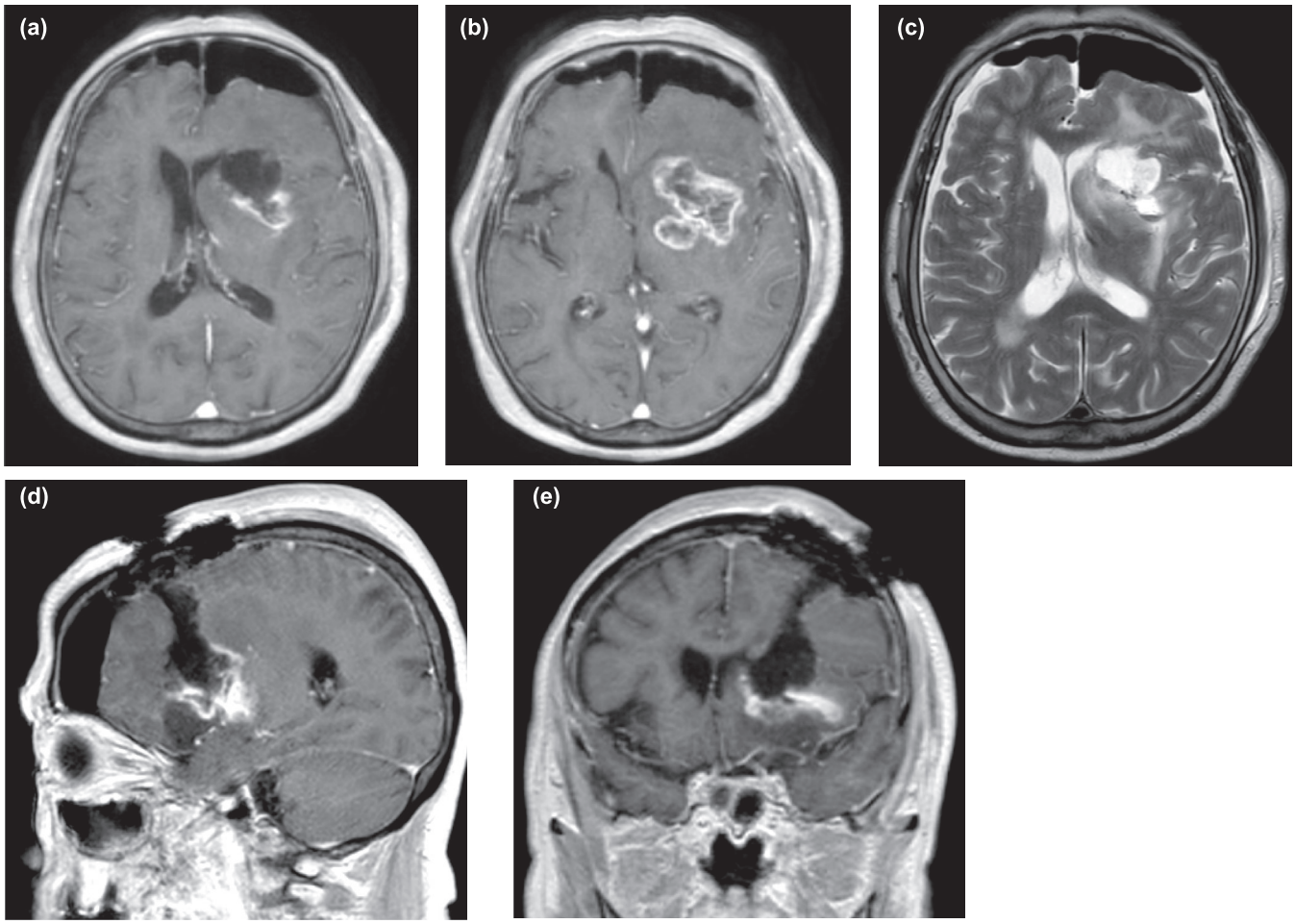

FIGURE 2 | Postoperative MRI. Postoperative brain MRI, revealing that partial removal (the superior-anterior part of the tumor) has been achieved on axial (a and b), sagittal (d), and coronal (e) post-enhanced T1WIs. The cyst has also shrunk on T2WI (c) and the mass effect is ameliorated. MRI, magnetic resonance imaging; WI, weighted image.

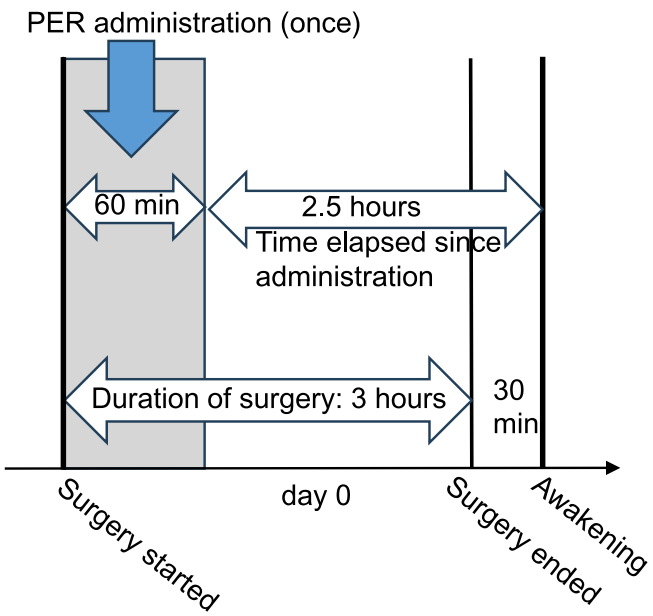

FIGURE 3 | Dosing course and serum concentration. An intraoperative time-lapse on day 0, the day of PER administration, is shown. Min, minutes; PER, perampanel hydrate.

Although there are reports that prophylactic administration of ASM significantly suppresses EPS [5], there is no consensus on prophylactic ASM for postoperative seizure control. Use, type, and duration of ASM therapy in actual clinical practice are currently entirely at the physician's discretion but, in Japan, short-term prophylactic administration is customarily used in supratentorial brain tumor surgery. If the administration of ASM is to be completed in one or 2 weeks, PER is an excellent choice from the standpoint of convenience and economy, as it remains effective for an extended period even with a single dose.

According to the package insert, PER is generally started at 2 mg because, based on the results of previous clinical studies, higher initial doses (up to 12 mg) increase adverse events such as floating dizziness and somnolence. We chose 6 mg of PER to increase efficacy but administered it under general anesthesia to reduce adverse events because it is impossible to feel dizziness or somnolence while anesthetized. Although the patient was advanced elderly (83 years old), anesthesia awakening was unremarkable and no postoperative adverse events occurred. Currently, the "poSTOP seizure-1 SF" study (an interventional study to evaluate the safety and feasibility of intravenous administration of 6 mg of PER during surgery in our institution [jRCTs031230730]) is underway. We are also planning a subsequent efficacy study and these results are eagerly awaited.

In conclusion, we report the first case of a single-dose, intravenous PER administration for EPS prophylaxis, rendering the patient EPS-free with no adverse events. A single 6 mg PER dose is convenient and may be one of the options for EPS prevention in brain tumor patients.

Author Contributions

Narushi Sugii: conceptualization, funding acquisition, writing – original draft. **Takeshi Yamada:** conceptualization, writing – review and editing. **Eiichi Ishikawa:** supervision, writing – review and editing.

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Ethics Statement

The prophylactic use of PER was approved by the Tsukuba University Clinical Research Review Board (approval number: TCRB23-026). We obtained written informed consent concerning participation in the research and publication.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data in this case report can be made available upon request. However, due to privacy and ethical constraints, some information may be restricted. Please contact the corresponding author if necessary.

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