CASE REPORT

Phenytoin Administration Following Early Postoperative Seizure After Brain Tumor Surgery

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ABSTRACT

Background: Early postoperative seizures (EPS), defined as seizures occurring within seven days following brain surgery, are a common and serious complication, particularly in patients with high-grade gliomas. EPS can prolong hospitalization, impair neurological recovery, and increase the risk of further brain injury. The optimal prophylactic strategy for seizure prevention remains controversial, especially in settings where access to second-generation antiepileptic drugs is limited.

Case: A 53-year-old female presented with progressive headaches and was diagnosed with a supratentorial intra-axial tumour consistent with high-grade glioma. She underwent subtotal tumour resection. Four hours postoperatively, the patient developed two episodes of generalized seizures. Immediate management included intravenous administration of midazolam, endotracheal intubation, and phenytoin administration. Diagnostic evaluations excluded metabolic or infectious causes. Near-infrared spectroscopy (NIRS) monitoring indicated stable cerebral oxygenation throughout the postoperative course. The patient experienced no further seizures and demonstrated full neurological recovery. Oral phenytoin was continued for 21 days.

Discussion: EPS are associated with multiple risk factors, including tumour location, size, and incomplete resection. In this case, the tumour's frontal and parietal lobe involvement, large volume, and subtotal excision likely contributed to seizure onset. Phenytoin, despite being a first-generation antiepileptic drug, proved effective in managing EPS and preventing recurrence in the absence of levetiracetam. NIRS served as a useful non-invasive adjunct to monitor cerebral oxygenation after a seizure.

Conclusion: Effective early recognition and treatment of EPS are critical in preventing secondary neurological complications. In resource-limited settings, phenytoin remains a viable monotherapy for seizure control post-craniotomy. Individualized, protocol-driven management strategies, supported by neuromonitoring tools such as NIRS, can optimize outcomes in brain tumor surgery.

Keywords: brain tumor; early postoperative seizure; ; phenytoin ; seizure management ; seizure prophylaxis

INTRODUCTION

Early postoperative seizures (EPS) are seizures that occur within the first seven days after a craniotomy procedure, whether for brain tumour excision or other methods. EPS can cause serious complications for the patient, like prolonged hospitalisation and decreased quality of life. The incidence of early post-craniotomy seizures, as demonstrated by epidemiological data, ranges from 4% to 40%, influenced by tumour characteristics, intraoperative surgical technique, and patient comorbidities.[1]

The aetiology of EPS following craniotomy brain tumor surgery is multifactorial. These include postoperative haemorrhage, cerebral oedema, infection, electrolyte disturbances, hypotension, and hypoxia. Furthermore, tumours that are large or located in epileptogenic areas, such as the frontal and parietal lobes, seem to increase the risk of seizures. Glioblastoma, a tumour that exhibits epileptogenic properties, is predisposed to induce seizures. Meanwhile, the part of the brain tumour that is left after brain tumour resection can increase the risk of seizure, because it can trigger epileptiform activity.[1,2]

Prophylactic antiepileptic use after brain surgery remains controversial and unstandardized due to limited high-quality evidence. Second-generation antiepileptic drugs, like levetiracetam, have been shown to exhibit an enhanced safety profile and a reduced incidence of neurocognitive side effects. However, these medications are not yet universally accessible in medical facilities, which hinders the attainment of optimal therapeutic outcomes. This discrepancy highlights the necessity for the development of postoperative seizure management strategies for patients with brain tumours. The implementation of such strategies is intended to enhance the quality of care provided to these patients and to improve their clinical outcomes.

CASE

A 53-year-old female patient, body weight 60 kilograms and height 163 centimetres tall, presented with complaints of severe headaches for six months, and the headaches became worse recently. No adverse effects such as visual impairments, vertigo, loss of consciousness, or convulsions were reported. No history of past illness such as hypertension, asthma, diabetes mellitus, or cardiovascular disease. The fasting history was adequate.

From the physical examination, the patient had with glasgow coma scale (GCS) score of $E_4V_5M_6$. The patient's blood pressure was 109/78 mmHg, pulse rate at 84 beats per minute, respiratory rate at 20 breaths per minute, body temperature of 36.6°C, and oxygen saturation (SpO2) of 97% room air. There were no observed issues related to the airway, respiratory function, or circulation. From the head and neck examination, there's no sign of anaemia, nor icteric sclera, with both pupil diameters measuring 3 mm. Slowed light reflexes and positive corneal reflexes were observed in both eyes. A physical examination of the nose, mouth, neck, lungs, heart, and abdomen was conducted; however, no abnormalities were detected. There are no abnormalities in motor function, sensory function, or coordination function.

The results of the routine laboratory investigations, including those of haematology, coagulation function, renal function, and electrolytes, were found to be within normal limits. Thoracic

imaging showed no cardiac or pulmonary abnormalities. A magnetic resonance imaging (MRI) examination of the head with contrast was conducted, which revealed the presence of a supratentorial intraaxial lesion measuring 4.6 x 4.2 x 5.5 cm. This lesion exhibited a solid cystic component, characterised by scaly, necrotic, and multiple age-related haemorrhages. The borders of the lesion were noted to be well-defined and irregular, extending from the left frontoparietal lobe to the right frontoparietal lobe. This extension resulted in subfalcine herniation to the right by 1.6 cm, accompanied by surrounding vasogenic oedema. The results of the MRI investigation indicated the presence of a tumour mass, which was suspected to be a high-grade astrocytoma, also known as glioblastoma. (Figure 1)

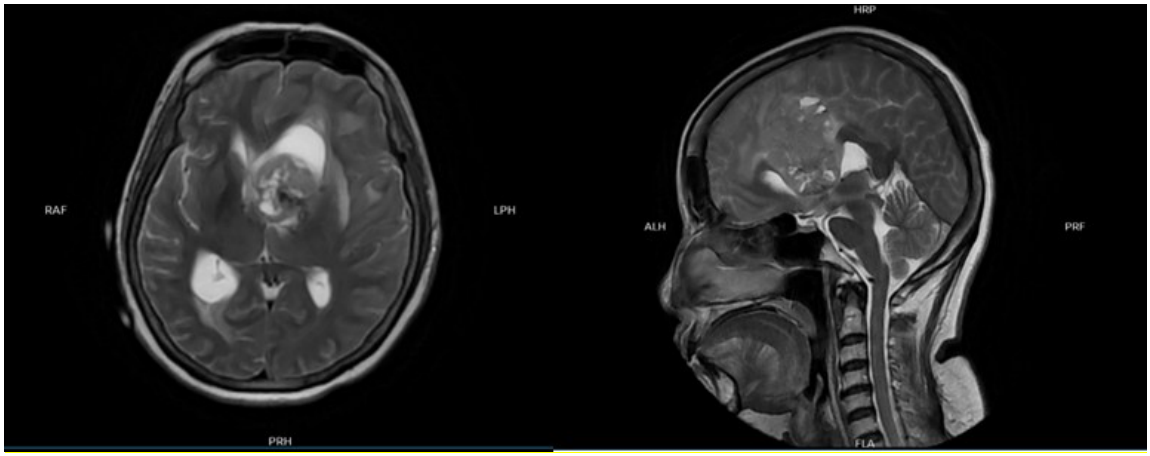

Figure 1. MRI examination of the head

The patient underwent a craniotomy tumour resection under general anaesthesia in ASA III physical status. The patient was administered a premedication of Paracetamol 1 g one hour before surgery. On the operating table, the patient was lying in a supine position, and we applied an electrocardiogram (ECG) with five leads, pulse oximetry, and non-invasive blood pressure. For induction, we gave a dose of dexmedetomidine at an initial rate of 1 microgram per kilogram of body weight for a period of 10 minutes. This was followed by a maintenance dose ranging from 0.2 to 0.7 micrograms per kilogram per minute, in conjunction with preoxygenation and the maintenance of adequate airway patency. The patient was induced using Schnider mode propofol with a target effect of 4-6 ng/ml, fentanyl 100 mcg, lidocaine 80 mg, and rocuronium 50 mg intravenously. Intubation was performed after the onset of drugs was achieved using a non-kinking endotracheal tube (ETT) no. 7.0. Following the insertion of an ETT, an arterial line was inserted under local anaesthesia on the right radial artery to monitor arterial blood pressure in real-time, and end-tidal carbon dioxide (EtCO2) was installed. Post-intubation haemodynamics were as follows: blood pressure 131/67 mmHg, pulse rate 85 beats per minute, ventilator mode pressure-controlled with volume guaranteed, tidal volume (VT) 280-300 ml, respiratory frequency (F) 13 beats per minute, I: E ratio 1:2, positive end-expiratory pressure (PEEP) 5 cmH2O, fractional inspired oxygen (FiO2) 40%, oxygen saturation (SpO2) 99%, and end-tidal carbon dioxide (EtCO2) 38 mmHg. The patient was then connected to a

central venous catheter in the right subclavian vein, and a urinary catheter was also inserted to monitor fluid adequacy. Maintenance during surgery was given dexmedetomidine 0.3 - 0.5 mcg/kg/min, propofol TCI Schnider mode with a target effect of 2-5 ng/ml, and rocuronium 10 mcg/kg/hour. Before the surgical procedure, a scalp block was conducted, using levobupivacaine 0.25%.

The administration of mannitol was initiated at a dose of 0.5 g/kg BW upon opening of the scalp. No significant increase in heart rate or blood pressure was observed during the procedures of head pinning, scalp incision, and duramater opening. The surgical procedure itself lasted for a period of four hours. The total input of fluid was 1200 ml, comprising 1000 ml of crystalloid and 200 ml of medication. The output was 1120 ml, consisting of 750 ml of urine, 250 ml of bleeding, and 120 ml of perspiration. Surgical findings revealed a tumour in the frontoparietal region measuring 4x5x5 cm, which was excised with an estimated 90% of the tumour removed. During the surgical procedure, the patient's haemodynamics remained stable, and the brain relaxation score was 2/4.

Extubation was performed in the operating theatre. Post-extubation, haemodynamic parameters were stable, and the patient was fully awake with adequate spontaneous respiration. Postoperative analgesics administered included paracetamol (1 g every 6 hours) and dexmedetomidine (0.2 mcg/kg/hour intravenously). Postoperative pain score was NRS 2/10. And for further evaluation, the patient was sent to the intensive care unit (ICU).

Following a period of four hours of treatment in the intensive care unit, the patient experienced a generalised seizure with decreased consciousness. This seizure manifested for a duration of two minutes and occurred on two occasions, with an interval of 10 minutes between each seizure. The patient was administered an intravenous injection of midazolam, with a dosage of 5 mg. Subsequently, the patient was intubated and administered a loading dose of Phenytoin 1 g over 20 minutes, followed by a maintenance dose of 100 mg over a period of 8 hours. The patient was fitted with near-infrared spectroscopy (NIRS) as a modality to determine the balance of brain oxygen demand and supply; the NIRS value was 70-73%. The patient's GCS score decreased to $E_3V_TM_4$ following the seizure.

In order to ascertain the underlying cause of the patient's seizures, a range of diagnostic procedures was conducted. These included electrolyte checks, routine blood tests, and infection screening, which entailed regular temperature monitoring and the administration of antibiotics. The patient received antibiotic therapy in the form of ceftriaxon 2 g injection administered at 24-hour intervals.

There were no seizures observed on the second day after surgery, and the GCS score increased to $E_4V_TM_6$. The patient was able to breathe spontaneously and was prepared for ventilator weaning. The results of the NIRS monitoring process demonstrated a percentage range of 77-78%. No further neurological deficits were observed.

The patient was extubated on the third day after surgery, and no seizures or neurological deficits were found. The patient was subsequently transferred to the high care unit (HCU), where she underwent treatment for a period of two days.

During the two-day stay at HCU, the GCS score was $E_4V_5M_6$, with no seizures, neurological deficits, or other complications. The patient was subsequently admitted to the general ward and discharged two days later. Following the administration of the antiepileptic medication, the patient was discharged and instructed to continue with the oral administration of 100 mg of Phenytoin every eight hours for a period of up to 21 days following the initial seizure.

DISCUSSION

According to the International League Against Epilepsy (ILAE), a seizure is defined as a transient event arising from abnormal electrical activity in the brain, manifesting as clinical signs or symptoms, including alterations in movement, behaviour, sensation, or consciousness.[3] Focal seizures are distinguished by the occurrence of electrical disturbances that are confined to a specific region within one of the brain's hemispheres. Focal seizures without impaired consciousness generally have a duration of less than one minute. Generalized seizures are characterized by the absence of focal onset, bilateral involvement of the cerebral hemispheres, and the occurrence of loss of consciousness.[4] The classification of seizures is a complex undertaking, with the broad spectrum of possible classifications including generalised tonic-clonic (grand-mal), tonic, clonic, myoclonic, myoclonic-tonic-clonic, myoclonic-atonic, atonic, and non-motorised, including absences.[4]

In the case of seizures occurring after surgery, seizure types can be classified into two categories: early postoperative seizure (EPS) and delayed postoperative seizure (DPS). The term "early post-surgical seizure (EPS) type" is used to denote seizures that occur within seven days following surgery, while "delayed post-surgical seizure (DPS)" refers to seizures that occur between seven and 60 days post-surgery. Such seizures are generally considered to reflect an acute medical or surgical condition that may require emergency treatment.[5] Risk factors for the occurrence of electrocution EPS include bleeding, incomplete tumour resection, infectious complications, and electrolyte disturbances, as well as cardiopulmonary disorders leading to hypotension and hypoxia.[5,6,7] In this particular case, the seizure exhibited the characteristics of EPS, given its duration of four hours following the surgical procedure.

This patient presents with several risk factors for postoperative seizures directly related to the tumour itself. The diagnosis of a high-grade glioma is a primary factor, as this tumour type is known to cause seizures in a high percentage of cases. The tumour's location in the right and left frontoparietal lobes is also critical, as this region is associated with a significantly elevated seizure incidence compared to other brain areas. Moreover, its large size (4.6 x 4.2 x 5.5 cm) can induce seizures through mass effect and compression of adjacent neural tissue.

Beyond the tumour's intrinsic properties, the surgical procedure adds another layer of risk. The patient underwent a subtotal resection, where 90% of the tumour mass was removed. This specific surgical approach, which leaves some residual tumour behind, has been identified in studies as being correlated with an increased probability of developing seizures after the operation.

The treatment of the patients should be guided by institutional protocols so that multiple team members can simultaneously initiate a series of steps, including airway assessment, breathing assessment, and circulation assessment, and management.[8,9] In such cases, the immediate implementation of intubation and ventilator insertion is crucial for the maintenance of airway and respiratory function, with meticulous monitoring of circulation parameters facilitated by invasive blood pressure monitoring.[9] A range of strategies exists for the management of seizure disorders, including the administration of antiepileptic medications and the identification and treatment of the underlying cause. It is imperative that treatment is initiated without delay and managed as a neurological emergency. It is imperative to recognise the signs of hypoglycaemia promptly, as it can result in severe consequences, including seizures and permanent damage if not addressed expeditiously.[9,10] A range of investigative procedures may be utilised to ascertain the occurrence of early seizures following cerebral surgery. These include laboratory investigations, which are employed to detect any metabolic disturbances. Blood gas analysis is also conducted to ascertain the presence of anoxia-hypoxia, while mandatory infection investigations are also integral to the diagnostic process. The utilisation of non-contrast head CT scans should be considered in the majority of cases. The presence of fever, leucocytosis, and neck stiffness on clinical examination should raise suspicion of central nervous system infection, and lumbar puncture should be performed. In this case, the current blood sugar, blood laboratory, and blood gas analysis showed no abnormalities.

Antiepileptic drugs are frequently categorised into two distinct groups: 'first generation' (e.g., carbamazepine, phenobarbital, phenytoin, primidone, and valproate) and 'second generation' (e.g., lamotrigine, levetiracetam, felbamate, gabapentin, topiramate, tiagabine, oxcarbazepine, zonisamide, and pregabalin).[11] Second-generation anti-epileptic drugs have been shown to exhibit reduced drug interactions and enhanced tolerability in comparison to first-generation anti-epileptic drugs, as evidenced by several studies. Nonetheless, the utilisation of second-generation drugs has been associated with the occurrence of psychiatric adverse effects, including depression, agitation, and psychosis.[12] First-generation anti-epileptic drugs, including carbamazepine, phenytoin, and valproic acid, have been demonstrated to induce drug interactions (e.g., accelerate dexamethasone metabolism) and are associated with neurocognitive impairment. Valproic acid has been associated with a range of coagulopathy symptoms, including thrombocytopenia. This may be exacerbated if the drug is used concomitantly with temozolomide chemotherapy.[11,12]

The utilisation of antiepileptic medications for post-craniotomy seizure prophylaxis in patients diagnosed with brain tumours remains a subject of considerable debate. The selection of

pharmaceutical agents, dosage, and duration of administration is subject to variation depending on the institutional policies of individual neurosurgeons and intensivists. In recent years, levetiracetam has emerged as the preferred first-line prophylaxis, providing consistent protection against seizures. A 2015 Cochrane review concluded that the evidence supporting the use of antiepileptic drugs as post-craniotomy prophylaxis is limited.[3] Furthermore, it is imperative to consider the psychiatric side effects of levetiracetam when evaluating its potential adverse effects in patients with psychiatric comorbidities.[13]

Benzodiazepines are the preferred agent for the termination of seizures. Lorazepam (0.1 mg/kg) can be administered as an initial anti-epileptic drug, with a success rate ranging from 59% to 65%. In this particular instance, the midazolam 5 mg dosage was utilised as the seizure termination agent. The administration of benzodiazepines must be accompanied by the administration of first-generation or second-generation antiepileptic drugs. In this particular instance, phenytoin was utilised as an anti-epileptic monotherapy agent. For phenytoin, the recommended initial dosage is 20 mg/kg intravenously, followed by a maintenance dosage of 5-7 mg/kg/day in two to three divided doses. The utilisation of phenytoin as anti-epileptic therapy is still regarded as efficacious as monotherapy in glioma patients with epilepsy, exhibiting a success rate of 72% in the initial six months of treatment.[14] During the patient's treatment period, no adverse effects of phenytoin were found.

NIRS is a non-invasive technique that has been utilised for the real-time monitoring of brain oxygenation and metabolism. In the context of intensive care, NIRS has been employed to detect seizures within the intensive care unit (ICU).[15] The working principle of NIRS involves the use of light in the near infrared range to measure oxygen saturation in brain tissue. The NIRS value, expressed as a percentage, indicates the amount of haemoglobin that remains saturated after passing through the tissue, with normal values ranging from 60-75%. An increase in cerebral metabolism has been demonstrated to result in a decrease in rSO2, particularly in the absence of an adequate increase in oxygen supply. NIRS is a technique that offers several advantages, including portability, the capacity to achieve high temporal resolution, and insensitivity to motion. Furthermore, NIRS can be used in conjunction with other diagnostic tools, such as an electroencephalogram (EEG), to provide a comprehensive understanding of seizures.[16] The patient was subjected to the NIRS test, the results of which revealed a satisfactory range (70-79%) until the patient was discharged from the ICU.

In patients with EPS who do not experience recurrent seizures in the monitoring period of up to 21 days post-seizure, phenytoin can be discontinued gradually. This phased discontinuation approach is important to reduce the risk of withdrawal symptoms and seizure rebound. The discontinuation process generally entails a gradual reduction in dosage over a period of days or weeks, contingent on the patient's response. In instances where the patient exhibits persistently elevated risk factors associated with seizures or a documented history of epilepsy, the discontinuation of treatment may necessitate re-evaluation.[12-14] In this case, oral phenytoin 100 mg was administered

every eight hours for up to 21 days post-seizure, after which a re-evaluation was conducted to determine the gradual tapering down of the medication until its complete discontinuation.

The present case report has several limitations. A significant constraint pertains to the absence of second-generation antiepileptic medications, including levetiracetam, within the hospital's pharmaceutical repertoire. This limitation restricts the available options for seizure prophylaxis therapy. Levetiracetam has been demonstrated to exhibit a superior safety profile and reduced incidence of neurocognitive adverse effects in comparison with phenytoin. Consequently, the absence of levetiracetam represents a significant impediment in the selection of the most efficacious therapeutic approach. Furthermore, the utilisation of NIRS as a method of monitoring brain oxygenation in post-seizure patients is not only non-invasive but has not been integrated with a comprehensive EEG examination, which could provide more information regarding epileptiform activity. However, through the implementation of early seizure management and meticulous patient monitoring, the patient's condition was effectively managed, leading to a favourable outcome without the occurrence of any secondary injuries.

CONCLUSION

The evaluation results showed that phenytoin as monotherapy was effective in preventing recurrent seizures in this patient. EPS following brain tumor surgery is a common complication in clinical practice and can lead to secondary brain injury if not appropriately managed. Proper and targeted management of early postoperative seizures positively impacts patient recovery, reduces further complications, shortens hospital stay, and improves quality of life.

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