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# Prophylactic Anticonvulsants in Patients Undergoing Craniotomy: A Single-Center Experience

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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**Background:** There is no consensus on the efficacy of seizure prophylaxis in patients undergoing craniotomy. Some studies show that antiepileptic use decreases the risk of seizures, but other studies do not support this. The present study investigated the role of antiepileptic drugs in patient undergoing craniotomy due to various intracranial pathologies.

**Material/Methods:** A retrospective review was performed in adult patients undergoing craniotomy between January 2013 and June 2017. Results of 282 patients who did not have a history of seizures and had craniotomies for various reasons were included. In all patients with craniotomy planned, prophylactic AEDs were initiated pre-operatively.

**Results:** The incidence of postoperative seizures was 17.7% when all craniotomized patients were considered. The most commonly used anticonvulsant agent was phenytoin (75.2%). No serious antiepileptic drug reaction occurred requiring cessation of treatment.

**Conclusions:** Prophylactic antiepileptic treatment of patients undergoing craniotomy should not be continued beyond the first perioperative week if there is no serious brain injury. The intra- or extra-axial placement of the tumor affects the prophylaxis. Further randomized controlled studies are warranted in the future to investigate the efficacy of these medications.

**MeSH Keywords:** **Anticonvulsants • Craniotomy • Epilepsy, Generalized**

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## Background

Seizure frequency increases after supratentorial craniotomy, and depending on the cause, 17–50% of patients have seizures at least once postoperatively [1–5]. Attempts have been made to reduce this rate by use of antiepileptic drugs (AEDs), but there is no consensus on the efficacy of seizure prophylaxis in these patients. Control of seizures is important to avoid unexpected complications and to improve outcomes in patients undergoing craniotomy. Some studies show that antiepileptic use decreases the risk of seizures [6,7], but others do not support this [2,3,8]. Prophylactic effects of phenytoin (PHT), carbamazepine (CBZ), phenobarbital (PB), valproate (VPA), and levetiracetam have been evaluated in the literature. The use of prophylactic AEDs for patients with brain tumor undergoing craniotomy is a common practice. In addition, controversies remain regarding the use of prophylactic AEDs in traumatic and non-traumatic brain injury [1,9–11]. Between January 2013 and June 2017, we conducted a retrospective study to determine the effectiveness of postoperative seizure prophylaxis in patients who underwent craniotomy procedures due to intra- and extra-axial brain tumors, as well as traumatic and non-traumatic brain injury.

## Material and Methods

All records of patients who underwent craniotomy procedures due to intra- or extra-axial brain tumors, as well as traumatic and non-traumatic brain injury in our institution between January 2013 and June 2017 were retrospectively reviewed. The records were scanned for specific data: sex, age, histopathology (tumor case), occurrence of seizures before surgery, use of an AED before surgery, use of seizure prophylaxis after surgery, and the occurrence of seizures before or after surgery. We enrolled 335 patients. We excluded patients with previous seizure history, antiepileptic drug use, craniotomy for any reason before the procedure, patients needing extra-cranial surgery, patients under 18 years old, and patients with missing data. There were 282 patients who met the criteria, of which 165 (58.5%) had intra-axial and 117 (41.5%) had extra-axial pathologies.

Prophylactic AEDs are initiated in all patients with craniotomy planned, in accordance with routine clinical practice. The daily dose of the prophylactic anticonvulsants was calculated using the World Health Organization-defined daily dose. The AED medications used were PHT, VPA, CBZ, and levetiracetam.

### Statistical analysis

SPSS 19.0 was used for statistical analysis. Descriptive statistics of qualitative data are shown by frequency and percentage and quantitative data are shown by median, minimum, and maximum values. Fisher's exact chi-square test was used for comparison of qualitative variables between groups, and P values below 0.05 were considered statistically significant.

**Table 1.** Demographic information.

| Variable | Number (%) or median (range) |
|---|---|
| Sex | |
| Male | 148 (52.48) |
| Female | 134 (47.52) |
| Age (years) | 46.7 (18–87) |
| Tumor | |
| Intra-axial | 95 (33.7) |
| Extra-axial | 56 (19.9) |
| Traumatic brain injury | |
| Epidural hematoma | 35 (12.4) |
| Subdural hematoma | 26 (9.2) |
| Intraparenchyimal hematoma | 25 (8.9) |
| Non-traumatic brain injury | |
| Aneurysm | 25 (8.9) |
| Intraparenchyimal hematoma | 13 (4.6) |
| Decompressive craniectomy | 7 (2.5) |
| Antiepileptic agent | |
| Phenytoin | 212 (75.2) |
| Valproate | 10 (3.5) |
| Carbamazepine | 18 (6.4) |
| Levetiracetam | 42 (14.9) |

## Results

Demographics for our patient population are shown in Table 1. Of the 282 eligible patients identified, 148 (52.48%) were males and 134 (%47.52) were females, with a median age at diagnosis of 46.7 years (range, 18–87). Most patients who underwent craniotomy were tumor patients (53.5%), 86 (30.5%) had traumatic brain injury, and 45 (16%) had non-traumatic brain injury. The most commonly used anticonvulsant agent was phenytoin (75.2%), followed by levetiracetam (14.9%), carbamazepine (6.4%), and valproate (3.5%). Preoperative prophylaxis was interrupted on day 7 in epidural-subdural hematoma and craniectomy cases if the patient did not have a seizure. In intraparenchymal hematoma and aneurysm surgery patients,





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**Table 2.** Seizure occurerence and follow-up.

| Variable | Number (%) or median (range) |
|---|---|
| Follow-up time (days) | 310 (3–1,225) |
| Time from surgery to seizure (days) | 120 (1–710) |
| Postsurgery seizure | |
| Tumor | |
| Intra-axial | 23 of 95 (24.2) |
| Extra-axial | 5 of 56 (8.9) |
| Traumatic brain injury | |
| Epidural hematoma | 1 of 35 (2.9) |
| Subdural hematoma | 4 of 26 (15.4) |
| Intraparenchyimal hematoma | 7 of 25 (28) |
| Non-traumatic brain injury | |
| Aneurysm | 4 of 25 (16) |
| Intraparenchyimal hematoma | 4 of 13 (30.8) |
| Decompressive craniectomy | 2 of 7 (28.6) |

prophylaxis was continued until blood disappearance was detected by imaging methods. In tumor cases (intra- and extra-axial), prophylaxis was interrupted if the patient has a seizure-free period of 1 week for extra-axial cases and 6 months for intra-axial cases postoperatively.

Postsurgery seizure findings were given in Table 2. In all patients with craniotomy planned, prophylactic AEDs were initiated pre-operatively. The follow-up time was 310 (range, 3–1225 days) days and time from surgery to seizure was 120 days (range, 1–710 days). In total, 50 of the 282 patients who underwent craniotomy for various reasons had postoperative seizures (17.7%), and 40 of 165 (24.2%) patients had seizures with intra-axial and 10 of 117 (8.5%) with extra-axial pathologies. The difference between the groups was statistically significant (p=0.001). Epileptic seizures were most frequently observed in patients with intra-axial tumor, intraparenchymal hematoma, and decompressive craniectomy (24.2%, 28.9%, and 28.6%, respectively). Patients with extra-axial tumor, epidural-subdural hematoma, and aneurysm surgery showed lower frequency of seizures (8.9%, 2.9%, 15.4, and 16%, respectively).

The most common adverse effects of AEDs were, nausea/vomiting, rash, ataxia, confusion, somnolence, headache, and irritability. These drug adverse effects were prevented by medication changes or drug adjustments. No serious AED reaction requiring cessation of treatment occurred. There were no deaths due to seizure or AEDs.

## Discussion

Seizures are undesirable conditions that affect quality of life, recovery, and length of stay. The actual incidence of epilepsy in patients who undergo craniotomy is not clear because of the multiplicity of pathologies and variety of operative procedures. Depending on the cause, 17–50% of the patients have seizures at least once postoperatively [1–5]. Extravascular leakage of blood components causes free radical generation, and ischemia/hypoxia causes disturbance of ion balance across cell membrane are the main mechanisms. The incidence of epileptic seizures has been reported to decrease with the use of AEDs in patients undergoing craniotomy. Prophylaxis is recommended in patients with a postoperative seizure risk higher than 15% [4]. It has been reported that use for longer than 6 months in patients without preoperative seizures is ineffective [12].

The use of prophylactic AEDs for brain tumor patients undergoing craniotomy remains controversial, although most neurosurgeons continue to use it. There is no clear indication that these drugs reduce the incidence of seizures [13,14]. Although long-term use is unnecessary and is not recommended by most authors, it is often used to interrupt the prophylaxis in patients who are seizure-free under AEDs [2,3,14,15]. Postoperative seizure frequency was 18.5% in brain tumor patients who underwent craniotomy in our study, and this is compatible with most studies in the literature [1–3,8,13–15].

Intracerebral hemorrhage (ICH) is the most devastating stroke subtype. In addition to primer redistribution, uncertainties remain in the management and prophylaxis of seizures. Although seizures are common after hemorrhage, the efficacy of prophylactic AEDs is controversial, although its use is widespread. Sheth et al. estimated that AEDs are used by experienced vascular neurologists and neurocritical care specialists in about 40% of patients with ICH [16]. Another study stated that prophylactic anticonvulsants were associated with reduced 90-day mortality and improved 90-day functional outcome [17]. There are no randomized controlled trials of seizure prophylaxis in patients with ICH. Although routine prophylaxis is not recommended because seizures may increase metabolic demand, hematoma volume, and midline shift, and are associated with worse outcome, it is not easy for most neurosurgeons to give up prophylactic AEDs [18,19]. The incidence of seizures in our study during the follow-up period was 28.9%, including ICH due to aneurysm rupture, which is higher than or similar to recent reports [16,20,21]. Two of 7 patients who underwent craniectomy due to cerebrovascular ischemic events had epileptic seizures. We think that this high rate of seizures in patients with decompressive craniectomy may be due to the small number of patients with ischemic brain damage.





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Epileptic seizures are an important complication, especially in patients with traumatic acute subdural hematomas. In these patients, craniotomy is known to increase the risk [9]. In our study, 4 of 26 patients (15.4%) had post-craniotomy seizures. Prophylactic AED treatment is suggested for a limited period of time in acute subdural hematomas [9]. There is no consensus on the use of prophylactic AEDs in patients with epidural hematoma. Only 1 of 35 patients had a post-craniotomy seizure in our study.

Conventional AEDs seem to be more effective in controlling early-onset seizures after craniotomy [4]. Of the 131 traumatic and non-traumatic patients in our study, 14 of the 20 seizures (70%) occurred in the first 7 days after craniotomy. Of the 151 tumor patients, 105 (69.5%) seizures were observed after 1 week. This difference may be a consequence of epileptogenic focus formation.

The diagnosis of seizures depends on either clinical seizure manifestation or seizure patterns on electroencephalography (EEG). In particular, subclinical seizures are one of the problems leading to delayed treatment and worse outcome [9]. There are studies on postoperative EEG in patients with seizures after craniotomy [2,9,18,21]. There are also publications that did not include EEG [3,4,14,15]. In our study, the diagnosis of seizures depended on only clinical manifestation, but lack of EEG is a limitation of our study.

The use of prophylactic AEDs after craniotomy remains controversial. An epileptic seizure worsens the outcome and most neurosurgeons continue to use prophylaxis. In addition, once a patient was prescribed a prophylactic medication, continuation of the drug was common, even if the patient remained seizure-free. Considering the risk of seizures and complications, prophylactic AEDs are routinely used clinically as a protocol in our practice.

According to our clinical experience, AEDs prophylaxis should be discontinued at 1 week if there is no seizure in patients with epidural-subdural hematoma without major brain injury. In intraparenchymal hematoma patients, AEDs continue to be available until blood disappearance is detected by imaging methods against epileptogenic focus risk of blood components. We also believe that the use of AEDs prophylaxis for 1 week in patients with previously uneventful craniotomized extra-axial tumor patients is safe, but use in patients with intraaxial tumors depends on the choice of the surgeon. In patients who had seizures pre- or postoperatively, the timing for withdrawal of medications follows the standard of general epilepsy management.

## Conclusions

This retrospective study presents a single center' s experience with prophylactic use of AEDs in patients who underwent craniotomy for various intracranial pathologies. Our study is limited by the small number of patients and the lack of EEG. Our analysis may not be sufficiently powered to detect the absolute use of prophylactic AEDs. Studies including better risk/benefit ratios with larger patient populations will provide more information about the prophylactic use of AEDs. Further randomized controlled studies are warranted in the future to investigate the efficacy of these medications.

### Conflict of interest

None

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