Prophylactic Antiepileptic Drug Use in Patients with Brain Tumors Undergoing Craniotomy

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■ BACKGROUND: **Prophylactic use of antiepileptic drugs (AEDs) for patients undergoing brain tumor surgery is common practice despite lack of clear evidence. We hypothesized that prophylactic AED (pAED) use did not affect seizure rates in patients with brain tumor who underwent craniotomy for tumor resection.**

■ METHODS: **A retrospective review was performed of 606 patients who underwent surgery for brain tumors from 2006 to 2013 at the University of Florida, excluding patients with preexisting seizure condition before tumor diagnosis. Data were analyzed to determine seizure incidence, AED use, and AED toxicities.**

■ RESULTS: **Most patients (81%) had no seizure on presentation. Eight patients did not present with seizure but had seizure postoperatively, and 9 patients did not present with seizure or have seizure postoperatively but did have seizure on follow-up. Despite not presenting with a seizure preoperatively, 208 patients (43%) were placed on pAED preoperatively, 313 patients (64%) were on AED in the postoperative period, and 274 patients (56%) remained on AED at discharge. The pAED use odds ratio for seizures was 1.3 (95% confidence interval, 0.5—3.4; $P = 0.599$). At last follow-up, 34% of patients with no seizure on presentation remained on pAEDs.**

■ CONCLUSIONS: **pAEDs did not significantly reduce postoperative seizures in patients with brain tumor in this analysis. In addition, pAED was often continued once prescribed even if the patient remained seizure free.**

INTRODUCTION

The incidence of seizure in patients with brain tumors is estimated to be 30%[1-6] and differs based on tumor histologic type, grade, and location.[7] No clear evidence supports seizure prophylaxis with antiepileptic drugs (AEDs) in patients with brain tumors, and the American Academy of Neurology recommends against prophylactic AED (pAED) use in patients with newly diagnosed brain tumors.[8] However, prophylactic use of postoperative AEDs for patients with brain tumor undergoing craniotomy is common practice. In this setting, the American Academy of Neurology recommends tapering and discontinuation of pAEDs after the first postoperative week in patients without seizures.[8]

In patients with traumatic brain injury, prophylactic use of AEDs has been shown to decrease the incidence of early seizures.[9] Up to 35% of patients undergoing craniotomy for nonacute traumatic disease experience postoperative seizures within the first week.[10] Therefore, several studies have evaluated the benefit of pAEDs for nontraumatic neurosurgical patients. A recent Cochrane database systemic review by Weston et al.[11] reviewed 8 randomized control trials that aimed to determine the efficacy and safety of pAED use in patients undergoing craniotomy for nontraumatic disease. The investigators concluded that there is no consistent evidence to suggest that pAEDs are effective in preventing postoperative seizures.[11] This systematic review included patients with nontraumatic disease rather than with brain tumors alone, who may be at further increased seizure risk compared with other nontraumatic diseases. Further investigation is warranted to determine whether postoperative pAED use offers a substantial benefit of seizure prophylaxis in the patient population with brain tumor undergoing craniotomy.

We aimed to evaluate surgical patients with brain tumor for pAED use, seizure outcomes, and AED-related toxicity. We

Key words
- Antiepileptic therapy
- Brain tumor
- Seizure prophylaxis

Abbreviations and Acronyms
AED: Antiepileptic drug
CI: Confidence interval
IDH: Isocitrate dehydrogenase
IPS: Inverse propensity score
pAED: Prophylactic antiepileptic drug
WHO: World Health Organization

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hypothesized that pAED treatment in patients with brain tumor undergoing craniotomy would not change seizure outcomes and would be associated with increased toxicity.

METHODS

Patient Selection

Institutional review board approval was obtained. A retrospective chart review was performed of consecutive patients with brain tumor who underwent surgery at the University of Florida from September 2006 to September 2013. Patients were identified by searching the appropriate current procedural terminology codes within the University of Florida billing database. Clinical information such as patient demographic information, surgical data, radiologic data, pathologic data including World Health Organization (WHO) tumor grade, medical profile, and laboratory values was collected for each patient. Inclusion criteria were all patients with intra-axial or extra-axial tumors. Exclusion criteria were preexisting seizure condition before tumor diagnosis. The data were analyzed to determine patients who did or did not present with seizures, pAED use, seizure incidence for patients who were and were not on pAEDs, and any adverse outcomes from AED use. AEDs included levetiracetam, phenytoin, carbamazepine, lacosamide, lamotrigine, clonazepam, lorazepam, topiramate, and diazepam.

Statistical Analysis

The SAS statistical software package (version 9.3.0 [SAS Inc., Cary, North Carolina, USA]) was used to calculate descriptive statistics and to compare the groups of patients who present with or without seizure on each variable and outcome of interest. A Student's *t*-test was used to compare the groups for age, and Fisher exact tests were used to compare the groups for all other variables.

For patients who did have seizure at presentation (and thus received therapeutic AED), we used logistic regression to estimate the odds ratio for seizures in patients who received pAED relative to patients who did not receive pAED. Because of the observational design of our study, we assessed edema, tumor type classes (astrocytoma WHO grade III; glioblastoma WHO grade IV; meningioma WHO grades I, II, and III; diffuse astrocytoma WHO grade II, oligodendroglioma WHO grade II, and metastasis), and tumor location (frontal, occipital, parietal, temporal, and infratentorial) as potential confounders of the pAED effect. Because of extremely low frequency of occurrence, diffuse astrocytoma WHO grade II and oligodendroglioma WHO grade II were dropped from further consideration. We first compared relative frequencies of the confounders between pAED and non-pAED patient groups using the χ^2 test or Fisher's exact test. Because of the relatively small number of seizures observed in our study ($n = 17$), we could not directly include all of the confounders in a seizure risk model without serious overfitting, which could lead to a biased estimate of the adjusted pAED effect on seizure risk. To assess the simultaneous impact of all confounders on the pAED odds ratio, we developed a pAED propensity score model[12] that included all the confounders as predictors of the probability that a patient would receive pAED treatment. We used the propensity scores (predicted probabilities) from this logistic regression model to generate inverse propensity score (IPS) weights.[12] IPS-weighted relative frequencies of the confounders indicated that IPS weighting achieved excellent covariate balance across all the confounders. We estimated a pAED odds ratio effectively adjusted for all of the confounders using IPS-weighted logistic regression.[12]

In a separate analysis, we used logistic regression to estimate the pAED odds ratio for seizures in the subgroup of patients with known isocitrate dehydrogenase (IDH) status. We then estimated an adjusted pAED odds ratio considering IDH status as a confounder.

Table 1. Patient Characteristics and Outcomes for all Patients ($n = 606$) and Based on Absence or Presence of Seizure at Presentation Preoperatively

	Overall (n = 606)	No Seizure (n = 490, 81.0%)	Seizure (n = 116, 19.0%)	*P* Value
Age (years), mean (standard deviation) Median (range)	54.0 (19.3) 58 (0—94)	54.1 (19.4) 58 (0—94)	53.8 (18.5) 59 (4—91)	0.861
Female	305 (50.1)	245 (50)	60 (51.7)	0.694
Neurologic signs at presentation	481 (79.0)	430 (87.2)	51 (44.0)	**< 0.0001**
Headaches	242 (39.8)	221 (44.9)	21 (18.1)	**< 0.0001**
Weakness	106 (17.4)	91 (18.5)	15 (12.9)	0.158
Sensory loss	28 (4.6)	24 (4.9)	4 (3.5)	0.511
Cranial neuropathy	171 (28.1)	161 (32.7)	10 (8.6)	**< 0.0001**
Gait/clumsiness	140 (23.0)	132 (26.8)	8 (6.9)	**< 0.0001**
Edema	375 (62.7)	308 (63.8)	67 (58.3)	0.272
AED preoperative	296 (48.8)	208 (42.5)	88 (75.9)	**< 0.0001**
AED postoperative	421 (69.4)	313 (63.8)	108 (93.1)	**< 0.0001**
AED at discharge	381 (63.4)	274 (56.3)	107 (93.9)	**< 0.0001**
AED preoperative, postoperative, or discharge	442 (73.1)	330 (67.5)	112 (96.6)	**< 0.0001**
AED at follow-up	214 (43.2)	145 (36.0)	69 (74.2)	**< 0.0001**

Values are number (%) unless otherwise indicated. Patients separated based on having a seizure on presentation (no seizure on presentation or seizure on presentation).
Bolded *P* values are statistically significant ($P < 0.05$).
AED, antiepileptic drug.

RESULTS

A total of 606 patients met inclusion criteria. One hundred and sixteen patients (19%) had seizure at presentation before surgery, and 490 patients (81%) did not have seizure at presentation. Patient demographics and clinical data for all patients based on whether or not the patient had a seizure on presentation are shown in Table 1. The mean age for all patients was 54.0 years, and 50.1% of patients were female. Overall, 79% of patients had neurologic signs at presentation, and not surprisingly, patients with no seizure on presentation were more likely to present with a neurologic deficit (87.2% vs. 44.0%, $P < 0.0001$). The