The Influence of Perioperative Seizure Prophylaxis on Seizure Rate and Hospital Quality Metrics Following Glioma Resection

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BACKGROUND: Antiepileptic drugs (AEDs) are frequently administered prophylactically to mitigate seizures following craniotomy for brain tumor resection. However, conflicting evidence exists regarding the efficacy of AEDs, and their influence on surgery-related outcomes is limited.

OBJECTIVE: To evaluate the influence of perioperative AEDs on postoperative seizure rate and hospital-reported quality metrics.

METHODS: A retrospective cohort study was conducted, incorporating all adult patients who underwent craniotomy for glioma resection at our institution between 1999 and 2014. Patients in 2 cohorts—those receiving and those not receiving prophylactic AEDs—were compared on the incidence of postoperative seizures and several hospital quality metrics including length of stay, discharge status, and use of hospital resources.

RESULTS: Among 342 patients with glioma undergoing cytoreductive surgery, 301 (88%) received AED prophylaxis and 41 (12%) did not. Seventeen patients (5.6%) in the prophylaxis group developed a seizure within 14 days of surgery, compared with 1 (2.4%) in the standard group (OR = 2.2, 95% CI [0.3-17.4]). Median hospital and intensive care unit lengths of stay were similar between the cohorts. There was also no difference in the rate at which patients presented within 90 days postoperatively to the emergency department or required hospital readmission. In addition, the rate of hospital resource consumption, including electroencephalogram and computed tomography scan acquisition, and neurology consultation, was similar between both groups.

CONCLUSION: The administration of prophylactic AEDs following glioma surgery did not influence the rate of perioperative seizures, nor did it reduce healthcare resource consumption. The role of perioperative seizure prophylaxis should be closely reexamined, and reconsideration given to this commonplace practice.

KEY WORDS: Antiepileptic, Epilepsy, Glioma, Prophylaxis, Quality, Readmission, Seizure, Tumor

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Seizures represent a challenging problem in up to 50% of patients harboring a brain tumor.¹⁻³ The risk of tumor-related seizures is amplified in patients undergoing

surgical resection, and may result in acute clinical deterioration, delayed neurological recovery, and decreased overall survival.⁴⁻⁷ The administration of prophylactic antiepileptic drugs (AED) in the perioperative period is common, though its effectiveness is unproven. Most studies have focused strictly on the relationship between AED administration and seizure incidence. In this study, we examine the effect of prophylactic AED administration not only on seizure rate, but also on common hospital quality metrics and healthcare resource utilization in a cohort of patients with glioma.

ABBREVIATIONS: AED, antiepileptic drugs; BTRE, brain tumor-related epilepsy; CT, computed tomography; ED, emergency department; EEG, electroencephalography; ICU, intensive care unit; KPS, Karnofsky Performance Scale; LOS, length of stay

METHODS

Patient Population

Between 1999 and 2014, adult patients (≥ 18 years) undergoing craniotomy for glioma resection were enrolled in an institutional tumor registry after obtaining informed consent. Relevant demographic and clinical data were recorded from presentation until last clinical follow-up. This study included all patients with glioma undergoing an open craniotomy for cytoreductive surgery with at least 12 months of follow-up or known date of death (if before 12 months). Patients undergoing tumor biopsy only without resection were not included. Institutional review board approval was obtained for this study (#030372).

Perioperative AED Administration

Individual surgeon preferences determined whether prophylactic AEDs were administered. A total of 4 cranial tumor surgeons treated this population. Two surgeons administer AED prophylaxis as a matter of routine while another does not. The remaining surgeon utilized prophylaxis in the first 12 years of the study, however, since 2012 has elected to withhold. Of note, beyond a history of prior seizure, the decision to administer or not administer prophylaxis was independent of patient-specific factors.

As per the default pathway of pro-prophylaxis surgeons, seizure-naïve patients prescribed prophylactic AEDs received 500 mg of levetiracetam (Brussels, Belgium) intravenously during induction and every 12 h thereafter for 7 days. Intravenous levetiracetam was replaced with the oral regimen as soon as it was tolerated. In patients in the prophylaxis cohort with a prior seizure history already receiving maintenance AEDs preoperatively, the above regimen was added to their baseline medications. For such patients, whose baseline regimen included levetiracetam, the drug dosage was increased postoperatively by 500 mg for 7 days. Thus, patients with brain tumor-related epilepsy (BTRE) receiving baseline, preoperative AEDs were considered in the prophylaxis group when their regimen was supplemented for 7 days postoperatively with an additional dose of levetiracetam twice daily. In occasional circumstances, at the surgeon's discretion formal neurology input was sought preoperatively to assist with perioperative antiepileptic medication management.

Outcomes Measurement

Patients were divided into 2 cohorts for outcomes comparison: those receiving perioperative AED prophylaxis and those not. The primary outcome was the development of a perioperative seizure. Secondary outcomes included length of hospital and intensive care unit (ICU) stay, discharge disposition, and 90-day emergency department (ED) visitation and unplanned readmission. Perioperative seizures were considered those that occurred within 14 days after the index surgery. In-hospital seizures were diagnosed as clinical events by staff members of the neurosurgical and neurocritical care teams. When occurring beyond the confines of direct medical observation, seizure designation followed the summation of witness and/or patient reports, and clinical findings (eg, tongue biting, urinary incontinence). When necessary, electroencephalography (EEG) and/or neurology consultation was obtained.

A series of subgroup analyses were performed between the 2 cohorts after isolating into 4 high-risk groups. These groups have been previously identified as carrying an elevated risk of BTRE: temporal lobe tumor location,^{8,9} prior seizure history,^{3,10,11} low-grade histology,^{8,9,12,13} and subtotal tumor resection.^{11,13,14} Our institution's extent of resection designations⁴ is designed to eliminate surgeon bias. Briefly, nongross

total resection (subtotal tumor resection and near total resection) is designated when either $< 99\%$ of the preoperative contrast-enhancing (high-grade tumors) or T2-hyperintense (low-grade tumors) volume has been removed, or when the senior neuroradiologist cannot rule out residual tumor.

Statistical Analysis

Parametric data were reported as mean $\pm$ standard deviation and compared via Student's *t* test. Nonparametric data were given as median (interquartile range) and compared via the Mann-Whitney *U* test. Normality of continuous data was evaluated using the Shapiro-Wilk test. Dichotomous data were initially compared via the χ^2 test and comparisons of binary variables with fields containing less than 5 frequencies were compared using the Fisher's exact test. A *P*-value $< .05$ was considered statistically significant. All statistical analyses were performed using IBM SPSS software version 23 (IBM, Armonk, New York). Study data were collected and managed using Research Electronic Data Capture (REDCap) tools hosted at Vanderbilt University Medical Center.¹⁵

RESULTS

Study Population

During the 14-year study period, 342 patients underwent primary resection for histologically confirmed glioma. The median (IQR) age was 55.5 years (27.9) and 56% were male. Over half (57%) were diagnosed with grade IV glioma, while an additional 14% were grade III. Just over a quarter of patients harbored low-grade tumors (I: 6%, II: 22%). Histological subtypes included astrocytoma (75%), oligodendroglioma (15%), ependymoma (6%), and oligoastrocytoma (5%).

Clinical Characteristics

Seizures were the most common primary presenting symptom (38%), followed by headache (21%), disturbances of cognition (15%), and focal neurologic impairment (12%). Forty-three per cent of patients experienced at least a single seizure at some point prior to surgical intervention; 5% had a prior seizure, but tumor diagnosis was made in the setting of symptoms other than seizure. Frontal (35%) and temporal (30%) lobes were more frequently involved than the parietal (20%) and occipital (4%) lobes.

Patients in the prophylaxis group were statistically similar to those in the nonprophylaxis group in all but 2 of the examined parameters. As expected, nearly half (48%) of patients in the prophylaxis group had a history of seizure, relative to only 5% in the nonprophylaxis group ($P < .01$; Table 1). Similarly, a greater proportion of patients in the prophylaxis group (30% vs 12%) had a temporal lobe tumor ($P = .02$). Otherwise, age, median Karnofsky Performance Scale (KPS) score, tumor histology and grade, and extent of resection were similar between both groups (Table 1).

Prophylaxis and Seizures

Postoperative AEDs were administered in 301 (88%) patients, while the remaining 41 (12%) received no form of seizure prophylaxis (Table 2). Among those in the AED cohort, 146 (43%) had

TABLE 1. Baseline Patient and Tumor Characteristics Stratified By Postoperative AED Administration and P-Values for 342 Patients With Glioma

Variable	AED prophylaxis, n = 301	No prophylaxis, n = 41	OR (95% CI) (IQR)	P-value
Age, median (IQR)	54.5 (40.1-68.9)	61.2 (50.2-72.1)		.72
Male sex (%)	170 (56.5)	22 (53.7)	1.1 (0.6-2.1)	.73
KPS, median (IQR)	80 (70-90)	75 (61.3-88.8)		.99
History of seizure	144 (48.2)	2 (4.9)	14.7 (3.5-62.3)	< .01
Temporal location	90 (29.9)	5 (12.2)	2.9 (1.1-7.6)	.02
Histology				.12
Astrocytoma	232 (77.1)	23 (56.1)		
Oligodendroglioma	46 (15.3)	6 (14.6)		
Oligoastrocytoma	15 (5.0)	1 (2.4)		
Ependymoma	8 (2.7)	11 (26.8)		
Grade				.20
I	12 (4.0)	8 (20.5)		
II	62 (20.7)	12 (30.8)		
III	46 (15.3)	3 (7.7)		
IV	180 (60.0)	16 (41.0)		
EOR				.59
STR	110 (36.5)	17 (41.5)		
NTR	103 (34.2)	13 (31.7)		
GTR	88 (29.2)	11 (26.8)		

AED, antiepileptic drug; EOR, extent of resection; GTR, gross total resection; IQR, interquartile range; KPS, Karnofsky Performance Scale; STR, subtotal resection.

TABLE 2. Characteristics of AED Prophylaxis

Characteristic	N (%)
Patients receiving AED postoperatively	301 (88)
Duration of AED administration, days (mean/median)	9.2/7.0
Drug	
Levetiracetam	212 (62)
Phenytoin	78 (23)
Lamotrigine	7 (2)
Oxcarbazepine	5 (2)
Valproic acid	5 (2)
Other	8 (3)
Adverse drug reaction	24 (8)
Dermatologic reaction	14 (4)
Decrease LOC	4 (1)
Electrolyte imbalance	1 (<1)
Other	5 (2)

AED, antiepileptic drug; LOC, level of consciousness.

a history of prior seizure. Of the 189 seizure-naïve patients, 155 (82%) received seizure prophylaxis perioperatively. Levetiracetam and phenytoin were the most commonly prescribed AEDs (62% and 23%, respectively), for a median duration of 7 days (mean 9.2 days). Adverse effects from AED were documented in 24 (8%) patients, most commonly manifesting as dermatologic reactions and decreased level of consciousness (5% combined; Table 2).

Within 14 days of surgery, 18 (5.3%) patients experienced at least 1 seizure (32 total ictal events). Among initial postoperative seizures, 8 were generalized tonic clonic, 5 were simple partial, and the remaining were complex partial or otherwise ill described. There was no significant difference in seizure rate between patients who received postoperative AEDs (5.6%) and those that did not (2.4%; $P = .68$; Table 3). Similarly, for patients without a prior seizure history, AEDs did not influence the postoperative seizure incidence (5.2% vs 2.9%, $P = .86$; Table 4). Nine seizures (28%) occurred beyond the median prophylaxis window (7 days) yet within the perioperative window (14 days), calling into question the optimal duration of AED prophylaxis.

Resource Utilization and Quality Metrics

The use of postoperative prophylactic AEDs had no influence on the rate at which the care team conducted seizure-related diagnostic testing. An EEG was conducted in 2 (4.9%) patients in the nonprophylaxis group, compared with 10 (3.3%) in the treated group ($P = .203$). Similarly, no difference was appreciated in the rate at which a seizure-related brain computed tomography (CT) scan (2.4% vs 5.9%, $P = .48$) or neurology consultation was obtained (2.4% vs 4.0%, $P = .76$).

Between the prophylaxis and nonprophylaxis groups, a similar median hospital (2 vs 3 days, $P = .054$) and ICU (2 vs 2 days, $P = .062$) length of stay (LOS) was observed. In addition, rates of unplanned 90-day ED visitation (20% vs 29%, $P = .116$) and

TABLE 3. Postoperative Events and Metrics Relative to Postoperative AED Administration and P-Values for 342 Patients with Glioma

Variable	AED prophylaxis, n = 301	No prophylaxis, n = 41	OR (95% CI)	P-value
Perioperative seizure	17 (5.6)	1 (2.4)	2.2 (0.3-17.4)	.680
Hospital LOS (d), med. (IQR)	2 (1-3)	3 (2-4)		.054
ICU LOS (d), med. (IQR)	2 (1.5-2.5)	2 (1-3)		.062
Discharge to home	217 (72.1)	32 (78.0)	0.7 (0.3-1.5)	.421
90-day ED visit	59 (19.6)	12 (29.3)	0.6 (0.3-1.2)	.116
90-day readmission	58 (19.3)	12 (29.3)	0.5 (0.3-1.1)	.140
Median OS, days (IQR)	404 (166-641)	489 (258-719)		.884

AED, antiepileptic drug; ED, emergency department; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; med, median; OS, overall survival.

TABLE 4. Postoperative Events and Metrics Relative to Postoperative AED Administration and P-Values for 189 Seizure-Naïve Patients With Glioma

Variable	AED prophylaxis, n = 155	No prophylaxis, n = 34	OR (95% CI)	P-value
Perioperative seizure	8 (5.2)	1 (2.9)	1.7 (0.2-13.7)	.855
Hospital LOS (d), med. (IQR)	3 (2-5)	3 (2-4)		.308
ICU LOS (d), med. (IQR)	2 (1-3)	2 (1-3)		.132
Discharge to home	101 (65)	26 (77)	0.5 (0.2-1.3)	.203
90-day ED visit	33 (21)	10 (29)	0.6 (0.3-1.5)	.306
90-day readmission	39 (25)	10 (29)	0.8 (0.3-1.9)	.609
Median OS, mo (IQR)	343 (127-560)	361 (157-566)		.623

AED, antiepileptic drug; ED, emergency department; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; med., median; OS, overall survival.

hospital readmission (19% vs 29%, $P = .140$) were not different between groups (Table 3).

Given that much of the current debate regarding seizure prophylaxis centers around patients without a prior seizure history, the same analysis was conducted among the 189 seizure-naïve patients and produced similar results (Table 4). Median hospital and ICU LOS were similar between groups (3 and 2 days, respectively; $P = .31$ and $.13$). The rates of 90-day ED visitation (21% vs 29%, $P = .31$) and 90-day hospital readmission (25% vs 29%, $P = .61$) were also similar. Discharge disposition and median overall survival figures were similar between the prophylaxis and nonprophylaxis groups, in both seizure-naïve and seizure-positive cohorts ($P > .2$; Tables 3 and 4).

High-risk Subgroups

High-risk groups included patients with a prior seizure history, temporal lobe tumor, subtotal resection, and low-grade histology. Among 94 patients with a temporal lobe tumor, 4 patients (4.5%) developed a perioperative seizure while on prophylaxis, compared with 0 not on prophylaxis ($P = .80$; Table 5). Sixteen patients (7.7%) with a subtotal resection on AED prophylaxis developed a seizure compared with 1 (3.4%) in the nonprophylaxis cohort ($P = .36$). Nearly all patients (97%) with a prior seizure history received perioperative prophylaxis, though a protective effect

against seizures could not be concluded ($P = .88$). And among 97 patients with a low-grade tumor, 7% on AED prophylaxis experienced a seizure compared with 0% not receiving prophylaxis ($P = .28$; Table 5). Of note, odds ratios were not calculated for comparisons in which one arm contained zero events (Table 5).¹⁶

DISCUSSION

In this institutional cohort of 342 patients undergoing glioma resection, the administration of perioperative AED did not reduce the incidence of postoperative seizure. The lack of a clinical benefit of prophylactic AED was demonstrated both in patients with and those without a prior seizure history. Furthermore, patients with a perceived elevated seizure risk, including those with temporal lobe tumors and brain tumor-related epilepsy, did not experience a lower perioperative seizure rate while receiving AED prophylaxis. In addition, prescribing AEDs in the perioperative period did not correlate—positively or negatively—with the acquisition of seizure-related investigations, including EEGs, CT scans, or neurology consultations. Finally, AED prophylaxis had no perceived influence on hospital or ICU LOS, discharge destination, or overall survival.

TABLE 5. Fourteen-Day Seizure Incidence and P-Values Among Patients With Elevated Risk for Brain Tumor-Related Epilepsy

High-risk group	AED post-op	No AED post-op	OR (95% CI)	P-value
Prior history of seizures	6.3% (9/142)	0% (0/2)	NA*	.88
Temporal lobe tumor	4.5% (4/89)	0% (0/5)	NA*	.80
Subtotal resection (STR and NTR)	7.7% (16/209)	3.4% (1/29)	2.2 (0.3-17.4)	.36
Low-grade tumor (I and II)	6.7% (5/75)	0% (0/22)	NA*	.28

AED, antiepileptic drug; NTR, near total resection; OR, odds ratio; STR, subtotal resection.

*ORs are not calculated when a zero event exists among the comparison arms.¹⁶

Seizure Prophylaxis Debate

The debate surrounding prophylactic AEDs in patients with a brain tumor is not a new one and has been the subject of numerous retrospective observational, prospective cohort, and randomized clinical studies. Indeed, a tremendous amount of evidence—with varying degrees of quality—has been published to fuel this debate.^{1,2,17-28}

A disconnect exists between the paucity of clinical evidence supporting the benefit of AED prophylaxis and the actual practice by neurosurgeons regarding prophylaxis administration.²⁹ Specifically, more than a half dozen randomized clinical trials have demonstrated no benefit to AED prophylaxis in this population.^{27,30-35} Accordingly, in 2000, the American Academy of Neurology released a report recommending against the use of prophylactic AEDs in patients with brain tumor.³⁶ Yet 5 years later, a survey of neurosurgeons found that more than 70% routinely prescribe prophylactic AEDs in the perioperative period.³⁷

The purpose of this report is not to exhaustively review the literature supporting and refuting the role of AED prophylaxis—nor is it to advocate for or against their use. Rather, the authors introduce an additional set of variables to this discussion that look beyond direct and immediate outcomes such as seizure occurrence and peri-ictal morbidity. Others have recently studied predictors of seizure occurrence following brain tumor surgery, though not as they relate to perioperative prophylaxis.^{11,38,39} Still others have measured unplanned readmissions following surgery, but without accounting for the role of seizure prophylaxis.⁴⁰ The only prospective trial of perioperative levetiracetam in patients with brain tumor was a single-arm study of 25 patients; naturally, development of a resultant treatment paradigm was not possible.¹⁷ Thus, this report constitutes the largest study of patients with glioma examining the relationship between seizure prophylaxis and seizure occurrence, and the only to correlate healthcare resources and common hospital quality metrics. At a time when healthcare dollars are shrinking, and looming reimbursement changes are poised to penalize hospitals and providers for adverse events, these findings are timely.^{41,42} Our hope is to enrich this discussion by bringing a new category of data to the discussion such that practitioners may make more informed decisions about the prescribing of prophylaxis and what

impact this decision may have on clinical and quality-related outcomes.

Resource Utilization

Even in the face of level I evidence demonstrating no seizure reduction with AEDs, it has been postulated that the use of prophylaxis may result in less frequent screening measures for seizure.³⁷ That is to say, when a clinical episode resembling seizure occurs and there is uncertainty, a practitioner may be more concerned for an ictal event if the patient is not receiving an antiepileptic agent. Thus, EEGs or CT scans or neurology consultation, it would seem, may be more frequently sought in a patient not on prophylaxis. Our data argue against this however as we detected no difference in the rate at which EEGs, CT scans, or neurology consultations were obtained between the 2 patient groups.

Similarly, it is conceivable that uncertainty regarding true seizure occurrence in a patient not receiving prophylaxis may lead a practitioner to keep the patient in the hospital—or the ICU—for a longer period for closer observation. This reasoning was also refuted by our results, which showed no significant difference between the prophylaxis and nonprophylaxis groups in either hospital or ICU lengths of stay.

Beyond just the administration or withholding of seizure prophylaxis is the uncertainty regarding the optimal prophylaxis window—7 days, 2 weeks, 6 weeks, or beyond.²⁹ In our population, over a quarter of perioperative seizures (28%) occurred beyond the prophylaxis window, and whether these seizures could have been avoided by prolonging AED therapy is unknown. While our 7-day prophylaxis results suggest that AED prolongation would not have prevented these seizures, it is nonetheless worthwhile considering. It seems that if prophylaxis is to target the period of highest seizure risk, pro-prophylaxis surgeons might consider a 14-day treatment duration based on our findings. Clearly, the optimal AED duration is unknown and future studies should seek to better elucidate the ideal prophylaxis window.

High-risk Patients

While some studies have failed to demonstrate prophylaxis efficacy, respondents and other trialists have aptly suggested

that targeting of high-risk subgroups would be more appropriate than enrolling all patients with a brain tumor regardless of pathology or location.^{1,17} In essence, targeting patients who are more likely to develop a seizure postoperatively, and disregarding those who are not, would increase the observed event rate, and reduce the sample size needed to demonstrate a relative benefit. While reasonable, our data lend little credence to this position, even when considering the imbalanced comparator subgroups in Table 5. Prophylaxed patients with a temporal lobe tumor were no more likely to avoid a perioperative seizure than those not receiving AEDs. The same was true for patients with low-grade histology or who underwent a subtotal resection. Even in patients with a prior seizure history—whom both neurosurgeons and neurologist largely agree may benefit from additional prophylactic perioperative AEDs—a statistical reduction in perioperative seizures was not observed.

Regarding these imbalanced comparisons (Table 5), the reader is cautioned against over concluding our results—particularly as they relate to patients with a seizure history and those with a temporal lobe tumor. Naturally, such high-risk patients were far more likely to receive prophylactic AED dosing, thereby shrinking the control subgroup and rendering the statistical output more susceptible to type II error. Accordingly, we are not suggesting that surgeons withhold prophylactic dosing for these high-risk patients based on the above findings. Rather, we emphasize that given the available evidence before us, a reduction in clinical seizures is not observed when prophylaxis is administered. Admittedly, these findings perhaps are less likely to alter the firmly held practices of a seasoned neurosurgeon, and instead more valuable in providing equipoise for a topic that is in need of stronger evidence. Indeed, such negative results on this topic are seldom encountered within the neurosurgery literature. But acknowledging their existence before our nonsurgical colleagues serves only to strengthen our credibility, regardless from which side of this debate one argues.

Limitations and Future Directions

The current study has several limitations, which must be carefully considered before extrapolating these results to all patients with postoperative brain tumor. This was a retrospective review of patient data thus exposing the results to several forms of bias. Treatment bias influenced a subgroup of these patients, as prescription rates were expectedly greater in patients with a prior seizure and those with a temporal lobe tumor. Some patients may have presented to an outside hospital after a seizure episode of which we did not become aware. In reviewing our and the oncologists' outpatient visits, these events were largely captured, though it is possible some were not, introducing a form of loss to follow-up bias. Also, while absence seizures were not witnessed in this population, their occurrence cannot be ruled out; thus, our overall seizure incidence may have been artificially low. Next, though the study was limited to patients with glioma who underwent cytoreductive surgery, there was still heterogeneity with more than 40% of patients with a prior seizure history. While including this BTRE population may dilute the assessment of AED

effectiveness in seizure-naïve patients, it did allow greater generalizability to all patients with glioma undergoing resection. Also, the limited number of patients within the nonprophylaxis arm of the high-risk subgroups limits the statistical reliability of certain results, and—in some scenarios—the ability to calculate meaningful odds ratios. This study describes the outcomes related to patients treated primarily with levetiracetam or phenytoin only; alternative well-tolerated agents such as lacosamide were not examined. Whether such agents could more effectively reduce perioperative seizures remains to be seen. Similarly, whether 500 mg is the optimal perioperative prophylaxis dose is unknown. It is conceivable that higher doses may have been met with greater seizure control. Lastly, because the seizure event rate is relatively small this study may have been underpowered to detect true differences among the population subgroups.

Few will argue the deleterious consequences of a postoperative seizure, and fewer the importance of minimizing their occurrence. Yet to unequivocally assert that administering prophylactic AEDs will achieve this end is to ignore the considerable evidence suggesting it does not. Still, the decision to administer perioperative AEDs will—and should—remain in the hands of the surgeon. Indeed, with such a well-tolerated drug in levetiracetam, if even a miniscule protective effect is believed, the use of AED prophylaxis will probably resume. Ultimately, the debate will likely continue until a definitive answer is provided by an adequately powered, randomized trial conducted with neurosurgeons and neurologists jointly.

CONCLUSION

In patients with glioma, the delivery of prophylactic AEDs had no influence on perioperative seizure rate, hospital LOS, or discharge status. In addition, the use of prophylaxis was not associated with a reduction in the acquisition of EEGs, CT scans, or neurology consultations. Until quality evidence demonstrates their value, neurosurgeons, neurologists, and neurocritical care physicians alike should reconsider the administration of prophylactic AEDs.

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COMMENTS

In this retrospective study, the authors examined whether prophylactic use of antiepileptic drugs (AED) prevented seizures after surgery in patients with brain tumors. The records of 342 patients undergoing surgery for resection of a glioma were reviewed. Use of AED was based on the preference of the 4 surgeons involved, yielding 301 patients (88%) who received prophylactic AED and 41 who did not. The medication of choice was levetiracetam, which, due to its accepted efficacy, ease and safety of administration, lack of need for blood levels, and fairly low side-effect profile has become the most commonly used AED on neurosurgical services in the US. For the 43% of patients who had sustained a prior seizure, levetiracetam was added to their regimen, or increased by 500 mg a day if they already were on that drug. There was no significant difference between the groups regarding age, KPS, tumor histology and

grade, and extent of resection. On the other hand, the prophylaxis group patients were more likely to have had a prior seizure (48% vs 5%) or a tumor in the temporal lobe (30% vs 12%), presumably a more epileptogenic site.

The risk of a seizure within 14 days was not reduced by the use of prophylactic levitiracetam. In addition, ICU and hospital lengths of stay were similar, along with rates of readmission, ER visits, and the use of EEG, postoperative CT, and neurology consultations. The authors do not reach a firm conclusion from this limited retrospective study, and wisely pull back from recommending against the use of prophylactic AED in patients having brain tumor surgery. Instead they end with the oft-heard call for a randomized clinical trial.

Neurosurgeons treating patients with brain tumors all have had the experience of early postoperative seizures occurring. The effects on individual patients can be profound. Even if there is no side effect of

increased intracranial pressure, the inability to drive for a minimum of 6 months (a year in many of the United States) can wreak havoc in the life of a patient and his/her family. Is there really sufficient equipoise to ethically undertake a randomized clinical trial of this issue? Would you withhold an AED from your patient in the days and weeks after craniotomy for brain tumor?

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In my opinion, this problem needs to be addressed in a more comprehensive way—but it is worth an extended review as well as some well designed further prospective studies.

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