Comparative analysis of monotherapy versus duotherapy antiseizure drug management for postoperative seizure control in patients undergoing an awake craniotomy

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OBJECTIVE Postoperative seizures are a common complication in patients undergoing an awake craniotomy, given the cortical manipulation during tumor resection and the electrical cortical stimulation for brain mapping. However, little evidence exists about the efficacy of postoperative seizure prophylaxis. This study aims to determine the most appropriate antiseizure drug (ASD) management regimen following an awake craniotomy.

METHODS The authors performed a retrospective analysis of data pertaining to patients who underwent an awake craniotomy for brain tumor from 2007 to 2015 performed by a single surgeon. Patients were divided into 2 groups, those who received a single ASD (the monotherapy group) and those who received 2 types of ASDs (the duotherapy group). Patient demographics, symptoms, tumor characteristics, hospitalization details, and seizure outcome were evaluated. Multivariable logistic regression was used to evaluate numerous clinical variables associated with postoperative seizures.

RESULTS A total of 81 patients underwent an awake craniotomy for tumor resection of an eloquent brain lesion. Preoperative baseline characteristics were comparable between the 2 groups. The postoperative seizure rate was 21.7% in the monotherapy group and 5.7% in the duotherapy group ($p = 0.044$). Seizure outcome at 6 months' follow-up was assessed with the Engel classification scale. The duotherapy group had a significantly higher proportion of seizure-free (Engel Class I) patients than the monotherapy group (90% vs 60%, $p = 0.027$). The length of stay was similar, 4.02 days in the monotherapy group and 4.51 days in the duotherapy group ($p = 0.193$). The 90-day readmission rate was higher for the monotherapy group (26.1% vs 8.5% in the duotherapy group, $p = 0.044$). Multivariate logistic regression showed that preoperative seizure history was a significant predictor for postoperative seizures following an awake craniotomy (OR 2.08, 95% CI 0.56–0.90, $p < 0.001$).

CONCLUSIONS Patients with a preoperative seizure history may be at a higher risk for postoperative seizures following an awake craniotomy and may benefit from better postoperative seizure control with postoperative ASD duotherapy.

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KEY WORDS awake craniotomy; seizures; antiepileptics; monotherapy; polytherapy; epilepsy; oncology

POSTOPERATIVE seizures occur in 17%–50% of patients who have a craniotomy for a brain tumor, depending on the tumor type, size, and location.^{3,6,7,13,16,19,24,44} These risks for perioperative seizures can increase following an awake craniotomy for tumor resection, where in addition to cortical manipulation to remove the tumor, eloquent regions of the brain undergo electrical stimulation for cortical mapping.^{18,38,42} Seizures following a craniotomy can lead to increased intracranial pressure, neurological decline, cerebral hemorrhage, or hypoxia.^{27,28,30}

From the patient's perspective, these complications can lead to longer hospitalizations, increased hospital costs, permanent morbidity, and diminished quality of life and have a negative effect on survival.^{9,17,33}

Antiseizure drugs (ASDs) following an awake craniotomy are important for the management of postoperative seizures, although there is varying evidence about their efficacy.^{16,19,26,28–30,34,43} Following cortical stimulation and tumor resection in an awake surgery, ASD management must be carefully handled. Inadequate ASD use may lead

ABBREVIATIONS ASD = antiseizure drug; KPS = Karnofsky Performance Status.

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to postoperative seizures, while overuse of ASDs may result in detrimental drug-related side effects.⁵¹ In addition, excessive ASD use can present additional costs to a patient.¹ As health care reimbursement focuses increasingly on postoperative morbidity and efficiency of care, it is important to determine the optimal postoperative management for seizure prophylaxis and treatment following an awake craniotomy.³⁹ Despite the evolution of ASDs and growing knowledge about tumor-related seizures, the optimal use of ASDs for postoperative seizure prophylaxis after an awake craniotomy remains unclear, as there are no evidence-based guidelines for their use in this setting.^{40,41}

In this paper, we aim to evaluate the efficacy of postoperative monotherapy and duotherapy of ASD regimens for postoperative seizure treatment following an awake craniotomy, to determine whether combinations of ASDs play a role in improved prevention of seizures after an awake craniotomy.

Methods

This study was approved by the Johns Hopkins institutional review board.

Patient Selection

A retrospective data analysis was conducted on 81 cases in which patients underwent an awake craniotomy for an eloquent intracranial lesion, or lesions involving areas of the brain that control speech, sensory, or motor function, between April 2007 and February 2016 and performed by a single surgeon (A.Q.-H.). Patients who received a single ASD for postoperative seizure prophylaxis or treatment were considered the monotherapy group, while patients who received 2 ASDs postoperatively were considered the duotherapy group. Patients who had a preoperative seizure history of 3 or more seizure events per month were selected to receive postoperative duotherapy, while patients with a preoperative seizure history of fewer than 3 events per month received monotherapy. All patients were either on ASD monotherapy preoperatively, or were given a single dose of an ASD (monotherapy) before surgery. Postoperative levetiracetam was dosed at 500–1500 mg every 12 hours, and postoperative phenytoin was started at 100 mg every 8 hours. Phenytoin serum levels were checked daily, and dosing was adjusted to obtain a normal serum level.

Postoperative Evaluation

All patients were evaluated for postoperative complications immediately after surgery, at the 1-month follow-up visit, and 6 months following surgery in an outpatient clinic. The Engel classification system was used to evaluate seizure outcome following surgery. The outcome was considered Class I if the patient was seizure free; Class II if he or she had rare seizures, less than 3 over the 6-month span; Class III if the patient had some improvement, with more than 3 seizures over the 6-month course; and Class IV if there was no improvement, with no reduction of seizures and possible worsening. Seizures were diagnosed by observation, clinical examination, or electroencephalography. The length of hospitalization was considered to be the period from the day of surgery until the day of discharge.

Tumor Volumetrics

The preoperative tumor volume was determined using either T1-weighted MRI with contrast or T2-weighted MRI (1.5- to 3-mm axial cuts) in addition to fluid-attenuated inversion recovery (FLAIR) axial cuts. The OsiriX software (Pixmeo) was used to determine the tumor volume by a clinician blinded to the cohorts, as we have previously described.^{4,5,14,15} The postoperative tumor volume was calculated using the MR images that were obtained 48 hours after surgery using the previously described methods. The extent of resection was calculated based on the formula (preoperative tumor volume – postoperative tumor volume)/preoperative tumor volume.

Statistical Analysis

Descriptive statistics were reported as numbers and percentages for categorical variables and means and standard deviations for continuous parametric variables. Parametric comparisons between 2 groups were performed using the 2-sample t-test, and nonparametric comparisons were performed using a rank-sum test. Categorical comparisons between the 2 groups (monotherapy vs duotherapy) were performed using Pearson's chi-square test. Associations with postoperative seizures were analyzed using logistic regression. The significance of differences was evaluated according to a Type I error-rate threshold of $\alpha = 0.05$. For the postoperative seizure risk factors, variables that had a p value < 0.1 on the univariate analysis were entered into a multivariate logistic regression analysis. A biostatistician contributed to the statistical analysis of this study (O.G.). All statistical analyses were done using STATA 14.

Results

Patient Population

Between January 2007 and February 2016, 81 patients with a supratentorial eloquent brain lesion underwent an awake craniotomy for the first time. All patients were given an ASD prior to surgery. Following surgery, 46 patients were treated with a single ASD (the monotherapy group). The other 35 patients were treated with 2 ASDs (the duotherapy group). All patients in the monotherapy group were treated with levetiracetam postoperatively. In the duotherapy group, 30 patients received levetiracetam with phenytoin as their postoperative duotherapy; 5 patients had a history of prior adverse reactions to phenytoin and were placed on an alternative duotherapy (3 patients had levetiracetam with valproic acid, and 2 patients had levetiracetam with lacosamide). The mean age was 49.1 years in the monotherapy group and 44.3 years in the duotherapy group ($p = 0.162$). Tumors involved the motor or sensory cortex, respectively, in 39.1% and 13.1% of the monotherapy group and 57.1% ($p = 0.108$) and 14.3% ($p = 0.872$) of the duotherapy group. Tumors involved the language cortex in 47.8% of the monotherapy group and 28.6% of the duotherapy group ($p = 0.079$). Glioma pathology accounted for 86.9% of tumors in the monotherapy group and 88.5% of those in the duotherapy group ($p = 0.827$). Additional tumor pathology and location comparisons were found to be similar between the 2 groups and are reported in Table 1.

The mean preoperative tumor volume was 45.3 cm³ and 52.5 cm³ in the monotherapy and duotherapy groups, respectively ($p = 0.253$). The mean postoperative tumor volume was 9.7 cm³ in the monotherapy group and 8.2 cm³ in the duotherapy group ($p = 0.762$). The mean extent of resection was 81.5% in the monotherapy group and 80.7% in the duotherapy group ($p = 0.923$).

Clinical Presentation

Preoperative seizures were present in 54% of the patients in the monotherapy group, and these patients had an average rate of 1.2 seizures per month prior to surgery. In the duotherapy group, 57.1% of patients had preoperative seizures ($p = 0.523$), with an average rate of 3.4 seizures per month ($p < 0.001$). The presentation of headache was found in 23.9% of the monotherapy cohort and 17.1% of the duotherapy group ($p = 0.459$). Focal motor/sensory deficits were present preoperatively in 10.9% of the patients in the monotherapy group and 12.2% of those in the duotherapy group, respectively ($p = 0.383$). Language deficits were seen in 37% of the monotherapy group and 42.9% of the duotherapy group ($p = 0.590$).

Postoperative Outcomes

The mean length of hospitalization was 4.02 days for the monotherapy group and 4.51 days for the duotherapy group ($p = 0.193$). Readmission to the hospital within 90 days of surgery occurred in 26.1% of the monotherapy group and 8.5% of the duotherapy ($p = 0.044$). The most common reasons for readmission for the 12 monotherapy patients were: seizures in 7 patients (58.3%), worsening aphasia in 2 patients (16.7%), altered mental status in 2 patients (16.7%), and sensory/motor changes in 1 patient (8.3%). Of the 12 monotherapy readmissions, EEG findings of seizure activity were found in 6 of the patients presenting with seizure, while 1 patient was observed to have seizure activity by a clinician. For the 3 duotherapy group readmissions, seizures were the most common cause for readmission, occurring in 2 patients (66.6%), followed by altered mental status, occurring in 1 patient (33.3%). For the 3 duotherapy readmissions, 1 patient had EEG findings of seizure activity and 1 was observed to have seizure activity by a clinician.

At the 6 months' follow-up, postoperative seizures had occurred in 21.7% of the patients treated with monotherapy and 5.7% of those treated with duotherapy ($p = 0.044$). In the monotherapy patients, 8 patients had postoperative seizures confirmed by EEG, 1 patient had seizure activity observed by a clinician, and 1 patient had family-reported seizure activity. In the duotherapy group, 1 patient had postoperative seizures confirmed by EEG and 1 patient had seizure activity observed by a clinician. For patients who had seizures after surgery, the average rate of postoperative seizures was 1.1 times per month in the monotherapy cohort and 1.0 times per month in the duotherapy cohort ($p = 0.343$). With respect to the patients with no preoperative seizure history (21 in the monotherapy group and 15 in the duotherapy group), there were no postoperative seizures seen within the 6 months following surgery in either cohort. Among the patients given postoperative

TABLE 1. Demographic and clinical characteristics of 81 patients who underwent an awake craniotomy for a brain lesion

Characteristic	Group		p Value
	Monotherapy (n = 46)	Duotherapy (n = 35)	
Age, mean (SD)	49.1 (15.7)	44.3 (14.3)	0.162
Sex			0.099
Male	26 (56.5)	26 (74.3)	
Female	20 (43.5)	9 (25.7)	
KPS, mean (SD)	95.0 (6.62)	93.4 (9.38)	0.157
Tumor location			
Language cortex	22 (47.8)	10 (28.6)	0.079
Motor cortex	18 (39.1)	20 (57.1)	0.108
Primary sensory cortex	6 (13.1)	5 (14.3)	0.872
Side			0.343
Left	37 (80.4)	25 (71.4)	
Right	9 (19.6)	10 (28.6)	
Pathology			0.399
Grade II glioma	16 (34.8)	11 (31.4)	
Grade III glioma	6 (13.0)	11 (31.4)	
Grade IV glioma	18 (39.1)	9 (25.7)	
Metastasis	1 (2.2)	1 (2.9)	
Cavernoma	4 (8.7)	3 (8.6)	
Abscess	1 (2.2)	0 (0.0)	
Tumor vol & EOR, mean (SD)			
Preop tumor vol, cm ³	45.3 (39.3)	52.5 (44.6)	0.253
Postop tumor vol, cm ³	9.7 (18.9)	8.2 (9.9)	0.762
EOR, %	81.5 (2.5)	80.7 (2.5)	0.923
Preop seizures	25 (54.0)	20 (57.1)	0.523
Focal	10 (21.7)	8 (22.9)	0.905
Generalized	15 (32.6)	12 (34.3)	0.874
Average per mo, (SD)*	1.2 (0.7)	3.4 (1.9)	<0.001
Intraop seizure	2 (4.3)	2 (5.7)	0.779
Postop seizures	10 (21.7)	2 (5.7)	0.044
Average per mo, (SD)*	1.1 (0.3)	1.0 (0)	0.343
LOS, mean (SD)	4.02 (3.95)	4.51 (8.96)	0.193
90-day readmission	12 (26.1)	3 (8.5)	0.044

EOR = extent of resection; LOS = length of stay.

Data are numbers of patients (%) unless otherwise indicated. Boldface type indicates statistical significance.

* Average number of seizures per month for patients who had seizures during the specified time period.

seizure prophylaxis with no prior preoperative seizure history, the mean duration of postoperative ASD treatment was 7.0 days in the monotherapy group and 9.3 days in the duotherapy group ($p = 0.412$). From the overall cohort, 69 patients (85.2%) had no postoperative seizures: 36 in the monotherapy group (78.2%) and 33 in the duotherapy group (94.3%, $p = 0.044$).

Evaluation at 6 months' follow-up, based on the Engel classification, showed that for the monotherapy and duotherapy cohorts, respectively, that outcomes were classified as Engel I (60% vs 90%), Engel II (4% vs 10%), Engel

TABLE 2. Distribution of postoperative AED treatment type and outcomes at 6-month postoperative follow-up for patients who had preoperative seizures

Type of Postop AED Tx	Engel Class at 6-Mo Follow-Up				p Value
	I	II	III	IV	
Monotherapy (n = 25)	15 (60.0%)	1 (4.0%)	7 (28.0%)	2 (8.0%)	
Duotherapy (n = 20)	18 (90.0%)	2 (10.0%)	0 (0.0%)	0 (0.0%)	
Total	33 (73.3%)	3 (6.7%)	7 (15.6%)	2 (4.4%)	0.027

Engel I = seizure free; Engel II = rare seizures; Engel III = worthwhile improvement; Engel IV = no worthwhile improvement; Tx = treatment.

The duotherapy cohort had a significantly greater percentage of patients with Engel Class I outcomes at the postoperative follow-up visit. Boldface type indicates statistical significance.

III (28% vs 0%), and Engel IV (8% vs 0%), ($p = 0.027$, Table 2).

Multivariate logistic regression demonstrated that patients with a preoperative history of seizures were more likely to have seizures following their awake craniotomy (OR 2.08 [95% CI 1.74–2.47], $p < 0.001$). Postoperative seizures in this study cohort were not found to be influenced by preoperative Karnofsky Performance Status (KPS), intraoperative seizures, tumor volume, tumor grade, extent of resection, type of ASD used, or tumor location (Table 3).

Discussion

Postoperative seizures following an awake craniotomy present a challenging complication that requires a good understanding about ASD management. In addition to the intraoperative cortical irritation, cerebral hypoxia, and hemorrhages that have been associated with causing seizures following a craniotomy, an awake craniotomy adds cortical electrical stimulation to map out eloquent regions of the brain, and this can also cause seizures.^{30,45,46} Intracranial pressure changes and brain shifts following surgery can also lower seizure thresholds, with the highest incidence of postoperative seizures found in the initial 48–72 hours after surgery.^{30,32,50} Our study shows that for patients who undergo an awake craniotomy and have a preoperative seizure history, postoperative ASD duotherapy can decrease the risk of seizures after the operation and reduce hospital readmissions compared with monotherapy treatment. We also show that a preoperative history of seizure is a significant predictor for seizures following an awake craniotomy.

Length of Hospitalization and Readmission

Postoperative seizures following brain tumor surgery have been shown to be associated with longer hospital stays and a higher likelihood of having a hospital readmission.^{11,35} In our study, we found that the length of stay was similar between the 2 cohorts, but that the monotherapy group had a higher rate of readmissions. The length of stay was slightly greater than 4 days for both of our cohorts likely due to the fact that observation in an inpatient set-

TABLE 3. Logistic regression for postoperative seizures for 81 patients undergoing an awake craniotomy for a brain lesion

Covariates	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Preop KPS score	0.99 (0.97–1.01)	0.112		NA
Preop seizure	1.31 (1.06–1.78)	0.046	2.08 (1.74–2.47)	<0.001
Intraop seizure	1.21 (0.88–1.65)	0.236		NA
Preop tumor vol	1.01 (1.00–1.02)	0.017		NS
Postop tumor vol	1.02 (1.00–1.03)	0.034		NS
EOR	0.78 (0.48–1.28)	0.316		NA
Grade II glioma	0.78 (0.59–1.02)	0.065		NS
Grade III/IV glioma	1.29 (0.98–1.69)	0.164		NA
Levetiracetam	0.95 (0.61–1.47)	0.798		NA
Phenytoin	1.08 (0.80–1.45)	0.606		NA
Motor cortex	1.05 (0.78–1.42)	0.731		NA
Sensory cortex	1.04 (0.74–1.47)	0.806		NA
Language cortex	1.11 (0.78–1.58)	0.540		NA

NA = not applicable; NS = not statistically significant.

Preoperative seizures were found to be a significant predictor for postoperative seizures following an awake craniotomy.

ting is often longer for patients who sustain a postoperative seizure. Often, following a postoperative ictal event, the patient requires neuroimaging, an electroencephalogram, and a neurology consultation. These measures can lengthen hospitalization and increase the hospital costs.¹⁵

Already, Medicare and Medicaid have implemented financial penalties for readmissions that are related to preventable morbidity.³⁹ In addition, the Affordable Care Act makes hospitals and surgeons accountable for patient care costs that are deemed to be avoidable.³⁹ Dewan et al.¹¹ found that patients with glioma surgery who had a postoperative seizure presented to the emergency department twice as often as those who did not (44% vs 19%). In our cohort, we found that following an awake craniotomy, patients who had a postoperative seizure and were treated with ASD monotherapy were 3 times as likely to require readmission as those who were treated with duotherapy (26% vs 8%). Given that our patient population all had surgery involving the eloquent language or sensorimotor regions of the brain, any type of surgical site inflammation or irritation would often elicit a seizure or noticeable symptom (i.e., aphasia/weakness) that would prompt the patient to go to the emergency department, where our institution often admits the patient for observation.

Dickinson et al.¹² reported that readmissions following brain tumor surgery often were caused by neurological symptoms that accounted for one-third (37%) of readmissions; the next most common reason for readmission in their study was infection (29%). We found that seizures were the most common reason for readmissions in our

patient cohort, accounting for nearly two-thirds of readmissions (58% in the monotherapy group and 66% in the duotherapy group). In contrast to the study by Dickinson et al., in our study, all of the patients who were readmitted had a preoperative seizure history; moreover, nearly half of our cohort (47%) had tumors near or involving the perirolandic motor region, which has been associated with higher perioperative seizure occurrence.^{14,22,38}

ASD Use

The literature has presented conflicting evidence regarding the efficacy of prophylactic ASD therapy, with some authors favoring ASD use^{26,34,43} and others against it.^{19,28,30} Despite the varying claims, most neurosurgeons use ASDs for seizure prophylaxis following a craniotomy.³³ Notable support for postoperative ASD use after a craniotomy include a randomized control trial by North et al.,³⁷ which showed that there was a significant reduction of postoperative seizures following a craniotomy using phenytoin for seizure prophylaxis. A retrospective analysis by Zachenhofer et al.⁵⁰ found that prophylaxis with levetiracetam also lowered seizure risk after a craniotomy for brain tumor. Conversely, Wu et al.⁴⁸ conducted a randomized controlled trial involving patients undergoing craniotomies for intraaxial brain tumors that did not show any difference in postoperative seizure occurrence with prophylaxis using phenytoin.

Early studies often used phenytoin to evaluate the efficacy of ASDs for seizure prophylaxis. The rate of adverse effects with phenytoin has been approximated at 15%. In addition, phenytoin also affects the metabolism of other medications, including chemotherapeutic drugs.^{9,36,49,50} Levetiracetam has been shown to have fewer side effects than phenytoin, with somnolence being the most common side effect. The reported rate of adverse effects for levetiracetam ranges from 5% to 27%, and it has no effect on the metabolism of other drugs.^{20,21,50} Our institution uses levetiracetam more than other ASDs following craniotomy. Studies have shown postoperative seizures rates of 1%–12% with the use of levetiracetam monotherapy for patients who have undergone surgical treatment of supratentorial lesions, but we have previously reported higher seizure activity in patients with perirolandic eloquent region tumors,¹⁴ which could explain our higher incidence of postoperative seizures in the monotherapy group (21%), in which nearly 40% of the patients had perirolandic lesions.^{2,20,35}

Duotherapy

For seizure management in general, monotherapy is used for newly diagnosed seizures, while duotherapy is considered if there is a failure of the monotherapy treatment.²⁵ In this study, we found improved postoperative seizure prophylaxis with the use of duotherapy compared with monotherapy for our patient population. This observation is likely due to the varying mechanisms of action of the 2 ASDs, as well as possible synergistic effects. The potential benefit of a synergistic effect from a combination of ASDs must be weighed against toxicity and unwarranted drug interactions.³¹ Since ASDs affect multiple ion channels and neurotransmitters, it is difficult to determine

what mechanism is responsible for the drugs' synergy. The mechanism of action for levetiracetam involves binding the synaptic vesicle protein 2A (SV2A), which provides a unique pathway that can improve the effect of other ASDs that target traditional mechanisms of augmenting the GABAergic or glutamatergic neurotransmission as well as those inhibiting sodium channels.²⁵ We tend to use levetiracetam and phenytoin as our combination of choice, given their different mechanisms of actions (phenytoin inhibits sodium channels), although future studies are warranted to look at other combinations of ASD use as well as the use of duotherapy for asleep craniotomies for brain tumor resection. Our general practice is to use postoperative duotherapy for patients who had a high frequency of preoperative seizures (≥ 3 or more per month). We did not find many side effects from our postoperative ASD use in either cohort. During the 6-month follow-up period, levetiracetam was discontinued prematurely due to complaints of lethargy in 1 patient in the monotherapy group (2.2%) and lacosamide was prescribed instead. In the duotherapy group, the drug combination was switched from levetiracetam and phenytoin to levetiracetam and lacosamide in 2 patients (5.7%) because of delirium in 1 case and thrombocytopenia in the other ($p = 0.403$).

Duration of ASD Use

In addition to the number of postoperative ASDs prescribed, the duration of postoperative ASD prophylaxis also varies from surgeon to surgeon, with 7 days often being the duration of prophylactic treatment for patients with no preoperative seizure history.¹⁰ Although prophylactic ASD treatment is used in the postoperative period to avoid complications of seizure, its efficacy in patients without a seizure history is uncertain in the literature.^{16,47} In a survey of members of the AANS/CNS Section on Tumors, 21% of neurosurgeon respondents reported using postoperative ASDs for ≤ 7 days, 35% for 2–6 weeks, and 36% for > 6 weeks.¹⁰ In our cohort, patients who had no preoperative seizure history were maintained, respectively, on postoperative monotherapy for 7.0 days and duotherapy for 9.3 days. Patients with a history of preoperative seizures or those who had postoperative seizures were maintained on monotherapy or duotherapy with the assistance of a neurology team, who determined the duration of the therapy.

Postoperative Seizure Predictors

In addition to the use of combination therapy, it is helpful to determine what other factors may influence the incidence of postoperative seizures following an awake craniotomy. Awake craniotomy is frequently performed in patients undergoing resection of lesions involving the perirolandic region of the brain, given the sensorimotor function in the area, and surgical treatment of lesions in this area been shown to increase the incidence of perioperative seizures.⁴² In our study, 47% of our patients had lesions involving the perirolandic region. Pathology and tumor location are also believed to influence the chance for seizure occurrence.²³ Preoperative seizures and low-grade gliomas have also been shown to increase the risk of postoperative seizures in patients undergoing craniotomy.^{23,24,35–37} Chang et al.⁸ reported that postoperative

seizures are less likely to be found in patients in whom gross-total resection was achieved. In our evaluation of perioperative factors that may influence the incidence of postoperative seizures, we found that preoperative seizure history had a significant association with postoperative seizures in our multivariate analysis. Although tumor volume and low-grade gliomas had a significant association with postoperative seizure in the univariate analysis, they were not found to be significant in the multivariate analysis. Given this information, duotherapy may benefit patients with a preoperative seizure history, who could be at a higher risk for postoperative seizures.

Limits of the Study

This study has limits that are inherent to retrospective studies. The Engel classification has previously been used for seizure analysis following tumor surgery;²⁴ however, in our study, the preoperative seizure frequency was lower in the monotherapy group than in the duotherapy group, which would make it harder to demonstrate postoperative improvement regarding seizure frequency in the former group. Because the duotherapy cohort had a higher preoperative frequency of seizures, reductions could be expected to be more noticeable. In addition, our reporting of postoperative seizures was derived from documented diagnosis based on observation, clinical examination, or electroencephalography, which may have increased the incidence of seizures found in our cohort.

Conclusions

An awake craniotomy is a complex procedure performed for the resection of tumors in eloquent regions of the brain, and it requires an intricate understanding of postoperative seizure management for these patients. Our study suggests that patients with a preoperative seizure history may be at a higher risk for postoperative seizures following an awake craniotomy and may benefit from reduced postoperative seizures with the use of ASD duotherapy.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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Conception and design: all authors. Acquisition of data: Eseonu, Eguia, Garcia. Analysis and interpretation of data: Quiñones-Hinojosa, Eseonu, Eguia, Kaplan. Drafting the article: Quiñones-Hinojosa, Eseonu, Eguia. Critically revising the article: Quiñones-Hinojosa, Eseonu, Kaplan. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Quiñones-Hinojosa. Statistical analysis: Eseonu, Garcia. Study supervision: Quiñones-Hinojosa, Eseonu.

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