Seizures in the perioperative period are a well-recognized clinical entity in the setting of brain tumor surgery. At present, the suitability of antiepileptic prophylaxis in patients following brain tumor surgery is unclear, especially in those without prior seizures. Given the paucity of tumor-type and site-specific data, the authors evaluated the incidence of postoperative seizures in patients with convexity meningiomas and no prior seizures.

Methods: The authors identified 180 patients with no preoperative history of seizures who underwent resection of a convexity meningioma. Some patients received antiepileptic prophylaxis for 7 days postoperatively while others did not, based on the practice patterns of different attendings. The rates of clinically evident seizures in the first 3–4 weeks after surgery were compared.

Results: Patients who received antiepilepsy drugs (129 patients) did not significantly differ from those who did not (51 patients) in terms of age, sex, WHO tumor grade, extent of resection, rate of previous cranial surgery or radiation therapies, or use of preoperative embolization. There was a single new postoperative seizure in the entire cohort, yielding a new seizure rate of 1.9% in patients not on antiepileptic prophylaxis compared with 0% in patients on antiepileptics (p = not significant).

Conclusions: While it is thought that the routine use of prophylactic antiepileptics may prevent new seizures in patients undergoing surgery for a convexity meningioma, the rate of new seizures in untreated patients is probably very low. Data in this study call into question whether the cost and side effects of these medications are worth the small benefit their administration may confer. (DOI: 10.3171/2010.5.JNS091972)
eases: meningiomas largely compress the cortex, whereas glioblastomas multiforme mainly infiltrate and/or destroy the neocortical tissues. Furthermore, in analyses authors often incorrectly assume that all brain tumors of a specific type are biologically similar in their seizure risks when markedly different surgical techniques are required to remove various tumor types located at distinct sites. It is probably too simplistic to combine seizure data from a patient undergoing an intradural subtemporal approach to remove a meningioma with data from a patient harboring a meningioma limited to the cerebral convexity, as the temporal lobe retraction necessary during surgery in the former case would probably alter significantly the seizure risk. For this reason, we present a case-control study limited to patients with no seizure history who underwent surgery for convexity meningiomas to estimate the natural rate of clinically apparent new postoperative seizures and to determine the relative effect of prophylactic AEDs.

Methods

Patient Population

All patients undergoing neurosurgical intervention at UCSF are prospectively enrolled in a database. Using this database, we identified all patients who underwent evaluation and treatment for meningioma at our institution between 1991 and 2009. From this cohort, we evaluated all patients who underwent, as their initial therapy, craniotomy for resection of a histologically proven convexity meningioma. We excluded all patients with a seizure history and those with extensive tumors extending well beyond the cerebral convexity, such as lesions invading the superior sagittal sinus or with significant involvement of the cranial base. This study was approved by the UCSF Committee on Human Research under the approval number H7828–29842–03.

Microsurgical Technique and Perioperative Management

Preoperative evaluation of all patients included T1- and T2-weighted MR imaging with or without contrast. Preoperative embolization was performed for larger tumors based on the discretion of the treating surgeon and when the supplying vessels were accessible for intravascular occlusion using polyvinyl alcohol particles. Standard microsurgical technique was applied.

Intraoperatively, all patients received Decadron (10 mg), mannitol (1 g/kg), and ceftriaxone (1 or 2 g) at the time of incision. Of note, no patient was on corticosteroid therapy prior to surgery. Postoperatively, all patients were cared for in a neurointensive care unit for 1 day before returning to the ward.

Some patients were placed on an antiepileptic agent at the time of surgery (Dilantin initially and Keppra more recently), which was continued for 1 week postoperatively and then discontinued if the patient was seizure free; others were not. Routine AED levels were checked in patients on Dilantin on postoperative Day 1 and every other day thereafter. The decision of whether to administer anticonvulsants postoperatively was made based on attending surgeon preferences. More specifically, 2 attending physicians (M.W.M. and M.S.B.) at our institution who operate on convexity meningiomas routinely place all patients on AEDs after resection, whereas 1 attending (A.T.P.) never puts any patient without a seizure history on AEDs. These differences form the basis of the current study. Medication records were reviewed to ensure compliance with the attending physician’s desired practice patterns, and attending physicians did not deviate from their practice patterns based on intraoperative impressions regarding the integrity of the cortex or pia.

Data Collection and Analysis

Clinical information was retrospectively reconstructed using patient medical records, radiological data, and pathological specimens from both UCSF and outside medical facilities. All clinical assessments were performed by a neurosurgeon. More specifically, postoperative evaluations were performed by both the attending and the residents at least daily while a patient was in the hospital and by the attending when the patient visited the clinic. Preoperative postcontrast T1-weighted MR images were reviewed to confirm tumor locations. Central pathology review was undertaken on the basis of the WHO II guidelines.

Information regarding the use of postoperative prophylactic antiepileptics and the incidence of postoperative seizures was reconstructed from a review of daily progress notes and medication administration records. An early-onset postoperative seizure was defined as any seizure event that occurred within 72 hours of surgery. A late-onset postoperative seizure was defined as a seizure event that occurred from after 72 hours postoperatively up to the routine follow-up clinic visit, which usually took place at 3–4 weeks postoperatively. Patients without clear follow-up documentation or inadequate documentation of their hospital course were excluded from our analysis. A seizure event was defined on clinical grounds, and our definition of seizure was made significantly broad to ensure we were not missing events that could reasonably be hypothesized to be seizures. Thus, a seizure event could include generalized seizure activity, partial motor seizure activity, episodic aphasia, notation of a clinical suspicion of complex partial seizures or a nonconvulsive status, or any neurological finding suspected to be seizure activity that was found not to be from another cause.

All data were compiled into an electronic database and cross-checked for accuracy before being subject to any statistical analysis.

Statistical Analysis

Continuous variables were compared using ANOVA after statistical tests demonstrated a Gaussian distribution of the data. Continuous data were expressed as the means ± SE. Between-group comparisons of binary variables were done using the Pearson chi-square. Significance was defined as a p < 0.05. All descriptive and statistical analyses were performed using SPSS, version 15.0 (SPSS, Inc.).

Results

Patient Demographics

Between 1991 and 2008, 188 patients with no history
Seizures after convexity meningioma surgery

of seizures underwent craniotomy for resection of a convexity meningioma at UCSF. Eight patients—6 on AEDs and 2 not on AEDs—did not return for their follow-up visit and thus were excluded from our analysis. Of note, none of these excluded patients had a known in-hospital seizure.

Demographic characteristics of these patients can be seen in Table 1. There was no significant difference in mean age, sex distribution, rates of previous craniotomy or intracranial radiation, or frequency of preoperative embolization between patients who received prophylactic AEDs versus those who did not. There was no significant difference in the distribution of WHO tumor grades between these 2 groups, suggesting that they did not differ much in the rate of aggressive and/or invasive tumor types that might require cortical manipulation or injury to remove completely. Moreover, the Simpson resection grade did not differ between patients taking AEDs and those not, suggesting that the degree of surgical aggressiveness was similar between the 2 groups.

**Rate of Postoperative Seizures in Patients Undergoing Surgery for Convexity Meningiomas**

One hundred twenty-nine patients were postoperatively given routine AED prophylaxis (Table 2). There were no episodes of early or late postoperative seizures in this study cohort. Additionally, no patient had a suspected seizure or underwent electroencephalographic testing to investigate a suspicion of seizure.

Fifty-one patients in our study were not given AEDs postoperatively. One of these patients (1.9%) with a large WHO Grade I convexity meningioma had a generalized tonic-clonic seizure on postoperative Day 3, which was likely preceded by a complex partial seizure episode. A workup including MR imaging of the brain and electrolyte studies did not reveal a contributing cause for the seizure. This patient was treated with levetiracetam, experienced no additional seizures, and had an otherwise uneventful postoperative course. He was discharged 2 days later. No other patient in this cohort experienced either early or late postoperative seizures.

Statistical tests did not reveal a significant difference in either early or late seizure rates between patients on and those not on AED prophylaxis postoperatively.

**Discussion**

In this study, we performed a retrospective case-control analysis of the rates of new-onset postoperative seizures in patients with no seizure history who underwent resection of convexity meningiomas. We found that patients without seizures before resection very rarely experienced new seizures in the 3–4 weeks after surgery, regardless of whether they were taking AEDs postoperatively. While no seizures occurred in patients taking AEDs, our results suggested that the rate of new-onset seizures following resection is very low at our institution, regardless of whether AEDs are used routinely. While AED prophylaxis can often reduce the incidence of seizures, AED administration probably does not entirely eliminate their risk. In fact, when studied in a large enough cohort, some seizures would be expected to occur in AED-treated patients. Thus, while the control group represents the best estimate of the rate of seizures in these patients, the complete absence of seizures in the treated group further emphasizes the low rate of seizures in patients with no prior seizures who are undergoing surgery for convexity meningioma.

The question of whether to routinely give AEDs to all patients undergoing brain tumor resection requires balancing a variety of known and potential risks, many of which are not well understood. On the one hand, it is undoubtedly desirable to avoid seizures during the recovery period following brain surgery given the potential serious and lasting consequences such as traumatic injuries, aspiration, or brain damage due to status epilepticus. On the other hand, routine prophylaxis with AEDs has had mixed results, and these medications unquestionably have significant side effects such as cognitive slowing, ataxia, and lethargy. These side effects can reduce a patient’s ability to participate in his or her own recovery and impair quality of life. Thus, a blanket statement of whether AEDs are good or bad for all patients undergoing craniotomy for a brain tumor is probably oversimplistic.

While our data suggested that the rate of seizures following surgery for convexity meningiomas is very low

<p>| TABLE 1: Summary of characteristics in 180 patients with convexity meningioma* |
|-----------------------------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No Postop AEDs</th>
<th>Postop AEDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of patients</td>
<td>51</td>
<td>129</td>
</tr>
<tr>
<td>mean age in yrs</td>
<td>58 ± 2.2</td>
<td>53 ± 1.5</td>
</tr>
<tr>
<td>% M/F</td>
<td>27/73</td>
<td>23/77</td>
</tr>
<tr>
<td>WHO grade (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>41 (80)</td>
<td>88 (69)</td>
</tr>
<tr>
<td>II</td>
<td>5 (10)</td>
<td>25 (19)</td>
</tr>
<tr>
<td>III</td>
<td>5 (10)</td>
<td>16 (12)</td>
</tr>
<tr>
<td>Simpson grade (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>32 (63)</td>
<td>70 (54)</td>
</tr>
<tr>
<td>2</td>
<td>14 (27)</td>
<td>45 (35)</td>
</tr>
<tr>
<td>3</td>
<td>2 (4)</td>
<td>8 (6)</td>
</tr>
<tr>
<td>4</td>
<td>3 (6)</td>
<td>6 (5)</td>
</tr>
<tr>
<td>preop embolization (%)</td>
<td>9 (18)</td>
<td>31 (24)</td>
</tr>
<tr>
<td>previous craniotomy (%)</td>
<td>4 (8)</td>
<td>18 (14)</td>
</tr>
<tr>
<td>previous radiation (%)</td>
<td>3 (6)</td>
<td>10 (8)</td>
</tr>
</tbody>
</table>

* For none of the characteristics was p significant.

**TABLE 2: Comparison of rates of early and delayed postoperative seizures in 2 patient groups**

<table>
<thead>
<tr>
<th>Seizure</th>
<th>No Postop AEDs</th>
<th>Postop AEDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>early postop</td>
<td>Yes 1 51</td>
<td>0 129</td>
</tr>
<tr>
<td>delayed postop</td>
<td>Yes 0 52</td>
<td>0 129</td>
</tr>
</tbody>
</table>

* p was not significant for either seizure type.
without medications, we think it is important to note that these rates might not necessarily extrapolate to surgery for other tumor types or for meningiomas located at different sites.\textsuperscript{5} Convexity meningiomas can generally be resected without the need for brain retraction or the sacrifice of significant cortical veins.\textsuperscript{23} Moreover, while microsurgical dissection is needed to separate these tumors from their interface with the pial surface, lower-grade convexity meningiomas generally do not invade the pia and cortex,\textsuperscript{2} and thus generally require less manipulation than intratumoral lesions, such as malignant gliomas. Therefore, more site-specific and tumor-specific data are needed to determine in which clinical situations AED prophylaxis is indicated.

At present, there are limited data regarding the appropriate duration of prophylactic AED therapy. We treated patients in this study with AEDs for only a total of 7 days postoperatively. The goal of AED therapy was to prevent early postoperative seizures during the immediate postoperative period, when the risk of seizures is probably elevated because of the recent cortical irritation. Given the side effects that AEDs can cause in these patients, it is difficult to justify administering AEDs for longer than a week to prevent the rare delayed postoperative seizures.

The major limitation of this study was the use of a retrospective chart review to determine the rate of clinically evident seizures. And while serious seizure events, such as generalized tonic-clonic seizures, do not seem to occur very often, we cannot rule out the possibility that these patients have subclinical seizures and that AEDs may reduce the incidence of these subclinical seizures. It is well known that subclinical seizures can occur in some patient populations,\textsuperscript{7} and the absent routine use of electroencephalography to detect seizures in this cohort prevents our detection of these events. Conversely, given that none of our patients has an altered mental status of unknown etiology, the clinical significance of whatever subclinical seizures were missed in our population is unclear. While the possibility of brain damage resulting from persistent untreated subclinical seizures exists,\textsuperscript{8,10,17,23} the incidence of this disease in noncomatose patients with no previously known seizure events is not well described. Thus, the long-term significance of missing subclinical seizures in these patients in unclear.\textsuperscript{13} Furthermore, the effect of AED administration on neural repair and recovery is unknown. Experimental evidence suggests that specific AEDs have a wide variety (usually detrimental) of effects on critical cellular and molecular events in the recovery of neural tissues following injury, including neurite differentiation,\textsuperscript{34,35} neurogenesis,\textsuperscript{14,27} and cellular proliferative pathways such as the extracellular signal-regulated kinase (ERK) and phosphatidylinositol-3-hydroxy kinase (PI3K) cellular signaling cascades.\textsuperscript{4} It is probably impossible to realistically reconstruct the cognitive side effect profile for these drugs in a retrospective fashion, as these side effects usually do not get recorded in the medical records. Thus, we did not attempt to analyze the risk/benefit ratio in this patient population. The ultimate net effect of using AEDs to prevent or treat subclinical seizures can only be determined using prospective studies with electroencephalography and neuropsychological testing, and such analysis is beyond the scope of the present study.

Furthermore, because this study is not prospective, the methods for detecting seizures will inherently differ between various attending physicians, and we are limited by differences in individual practice patterns and methods for detecting seizures between assorted physicians. Moreover, the timing of seizures has not been well described, and it is possible that delayed seizures could occur beyond the follow-up period. In our experience, it is very uncommon for new-onset seizures to develop in patients with meningioma more than a month after an eventful surgery; anecdotally we have found this to be especially true for benign convexity meningiomas. Thus, while a longer duration of follow-up might capture a few more new seizures, especially if studied in a large cohort, we would suggest that the extent of underestimation is likely low.

Conclusions

In summary, we demonstrated that while patients who routinely receive AEDs following surgery for convexity meningiomas do not experience new, clinically evident postoperative seizures, the rate of seizures in untreated patients undergoing this surgery is very low at our institution. Thus, although the routine use of prophylactic AEDs might prevent new seizures in patients undergoing surgery for a convexity meningioma, the rate of new seizures in untreated patients is very low. These data call into question whether the side effects of these drugs are worth the small benefit their administration may confer and suggest that a formal prospective randomized trial is warranted to definitively answer this question. Based on the between-group differences in the present study, we performed a power calculation. To appropriately power a study to demonstrate a 1.9% difference with 80% power and an $\alpha < 0.05$, a study would need to include 478 patients per group, or 956 patients total. This figure is about 75% of the total number of meningiomas at all locations treated at our institution over a 20-year period and is 6 times the number of convexity meningiomas treated in the present study. We question whether such a study is logistically feasible without extensive multiinstitutional collaboration. Until such a study is performed, these data provide a source of available evidence regarding the appropriateness of AED prophylaxis.
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Acknowledgments

The authors thank Meningioma Mommis for their support in facilitating long-term outcome research.

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Please include this information when citing this paper: published online June 25, 2010; DOI: 10.3171/2010.5.JNS091972.
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