Journal of Neuro-Oncology (2005) 74: 211–215
DOI 10.1007/s11060-004-6912-4

Clinical Study

Results of a survey of neurosurgical practice patterns regarding the prophylactic use of anti-epilepsy drugs in patients with brain tumors

Vitaly Siomin[1], Lilyana Angelov[1], Liang Li[2] and Michael A. Vogelbaum[1]
[1]*Department of Neurosurgery and* [2]*Department of Biostatistics and Epidemiology, Brain Tumor Institute, Cleveland Clinic Foundation, Cleveland, Ohio*

Key words: anti-epileptic drugs, brain tumors, prophylactic practice patterns

Summary

Introduction: The American Association of Neurology issued guidelines discouraging the prophylactic use of anti-epilepsy drugs (AEDs) in patients with brain tumors. We surveyed neurosurgeons to evaluate practice patterns with regard to using AEDs in neurosurgical patients with brain tumors. *Methods*: The survey consisted of 18 questions. Two group email blasts containing an internet link to the survey were sent to members of the American Association of Neurological Surgeons with email addresses. Uni- and multi-variate analysis of the responses was performed using t-test, Fisher's exact test, or chi-squared test, where appropriate. *Results*: The response rate was 15.5% (386/2491). The majority of respondents (270/386; 70.0%) had more than 5 years of experience in neurosurgery. Most respondents described their practices as general (224/379; 59.1%); about one-third were members of the Joint Section on Tumors (136/381; 35.7%). More than 70% of respondents reported routine use of AED prophylaxis for patients with intra-axial gliomas or brain metastases. AED prophylaxis was also routinely used for extra-axial benign tumors or stereotactic biopsies by 53.8% and 21.4%, respectively. On multivariate analysis, the number of years in practice of ABNS certified neurosurgeons was the strongest predictor for the use of AED prophylaxis. *Conclusions*: Routine use of AED prophylaxis in patients with brain tumors undergoing neurosurgical procedures remains the prevailing practice pattern among members of the AANS. Additional larger prospective studies with appropriate patient stratification culminating in development of neurosurgical guidelines on AED prophylaxis in brain tumor patients is warranted.

Introduction

Seizures are a common manifestation of brain tumors. Twenty to 40% of all brain tumor patients experience a seizure prior to diagnosis and at least 20–45% more will develop seizures at some point throughout the course of the disease [1–7]. There is little debate about the use of anti-epilepsy drugs (AEDs) once a seizure has occurred as the risk of future seizures are predictable in this setting. Whether AEDs should be used in patients who have a brain tumor but no prior history of seizures remains an open question. A number of studies have attempted to answer this question [1, 2, 4, 6–11]. However, the use of different patient populations, epidemiologic techniques, and outcome measures have prevented the physicians who treat patients with brain tumors from reaching a consensus regarding the role of prophylactic AEDs. A critical analysis of the medical evidence supporting the use of prophylactic AEDs was performed by the American Academy of Neurology. The product of this effort was the publication, in the year 2000, of a set of guidelines which discouraged the prophylactic use of AEDs in brain tumor patients [12]. It was the impression of the senior author of this report (MAV) that most neurosurgeons continue to use prophylactic AEDs for most brain tumor patients who undergo a surgical procedure. In collaboration with the American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (CNS) Joint Section on Tumors and with the technical support of the AANS, a survey of the AANS membership was performed to evaluate practice patterns with regard to the use of AEDs in neurosurgical patients with brain tumors.

Methods

Participants

All AANS neurosurgeons (regular and resident members) who had previously provided their email address to the AANS were contacted to participate in the study. Two email blasts containing an internet link to the survey were sent to 3249 surgeons. Of those, 758 surveys were returned due to an incorrect email address, which left a total of 2491 potential respondents. The survey link was active between January 14 and January 30, 2004, at which point the survey was closed.

Survey

The survey consisted of 18 questions. All respondents received the same set of questions, which focused on the use of AEDs in the following areas of surgical management of brain tumors: (1) surgery for benign

extraaxial brain tumors; (2) surgery for low-grade intra-axial brain tumors with a transcortical approach; (3) surgery for high-grade intra-axial brain tumors with a transcortical approach; (4) surgery for brain metastasis and (5) stereotactic brain biopsy. Respondents were also asked to indicate the size of their community (i.e. rural, small urban center of less than 1 million population; large urban center of over 1 million population), number of years in practice, status of ABNS certification, type of practice (i.e. solo, small private practice group of 1–3 surgeons, large private practice group of 4 or more surgeons, or academic center), degree of specialization, membership in the AANS/CNS Joint Tumor Section, the total number of surgical procedures per year, the percentage of brain tumor cases of the total number of cases, and whether they performed epilepsy surgery on the regular basis.

More specific questions about AED prophylaxis were asked as well, such as the time of discontinuation, monitoring, and adjustment of drug level, use of EEG prior to discontinuation of AEDs, whether the patients were referred to a neurologist, and when the AEDs were discontinued if a patient had perioperative seizure.

Statistical analysis

Uni- and multi-variate analysis of the responses was performed using *t*-test, Fisher's exact test, or chi-squared test, where appropriate. This project was funded by the AANS/CNS Joint Section on Tumors and technical support was provided by the AANS.

Results

Characteristics of the participant sample

Out of the 2491 electronically- contacted surgeons, there were 386 completed surveys available for analysis (15.5% response rate). Not all questions were answered by all respondents. A summary of the characteristics of the respondents is shown in Table 1.

The majority of respondents (270/386, 70%) had more than 5 years of experience in neurosurgery. Most respondents described their practices as general (224/379, 59.1%); the remainder had a focused, subspeciality neurosurgical practice (154/379, 40.6%). The majority of respondents practiced in an academic setting (187/384, 48.7%); of the remaining 197 respondents, 97 (25.3%) were in large private practice groups, 61 (15.9%) belonged to small private practice groups and 39 (10.2%) had solo practices.

Approximately one-third of respondents were members of the Joint Section on Tumors of the AANS/CNS (136/381, 35.7%). The majority (289/382, 77.6%) of respondents did not describe themselves as epilepsy specialty surgeons. However, one-quarter of respondents (93/382, 24.4%) indicated that they perform epilepsy surgery on a regular basis.

Overall, more than 70% of respondents reported routine use of AED prophylaxis for patients with intra-axial gliomas (77.7% in patients with high-grade gliomas and 74.0% in low-grade gliomas, 59.8% for awake craniotomy with electrocorticography) or brain metastases (70.8%). AED prophylaxis was also routinely used

Table 1. Summary of the characteristics of the respondents

Question	Total number of responses	Response subgroups	Number (percentage) in each response subgroup
1. Size of community	383	Large Urban	206 (53.8%)
		Small Urban	164 (42.8%)
		Rural	13 (3.4%)
2. Number of years in practice	386	Fellow/Resident	34 (8.8%)
		≤5 years	82 (21.3%)
		6–10 years	75 (19.4%)
		11–15 years	53 (13.7%)
		>15 years	142 (36.8%)
3. ABNS board certified?	385	Yes	279 (72.5%)
		No	106 (27.5%)
4. Type of practice	384	Solo	39 (10.1%)
		Small private	61 (15.9%)
		Large private	97 (25.3%)
		Academic	187 (48.7%)
5. Degree of specialization	379	General neurosurgeon	224 (59.1%)
		Subspecialized	155 (40.9%)
6. Epilepsy surgeon?	382	Yes	93 (24.4%)
		No	289 (75.6%)
7. AANS/CNS Joint Section member?	381	Yes	136 (35.7%)
		No	245 (64.3%)
8. Number of surgical cases in 2002		Median	250
		Average	249.6
		Range	10–800
9. Percent tumor craniotomies or biopsies		Median	15%
		Average	23.2%
		Range	0–100%

for extra-axial benign tumors or stereotactic biopsies by 53.8% and 21.4%, respectively.

Univariate analysis

For *intra-axial low-grade* ($n = 366$ replies) and *high-grade tumors* ($n = 367$ replies), *brain metastases* ($n = 363$ replies), and *stereotactic biopsies* ($n = 351$ replies), we found no statistically significant difference in the use of prophylactic AEDs on univariate analysis with regard to the surgeons' years in practice, ABNS certification, type of practice, degree of specialization, whether or not epilepsy surgery was part of the regular practice, AANS/CNS Joint Tumor Section membership and the percentage of brain tumor cases of the total number of cases.

Awake craniotomy with functional mapping ($n = 274$ replies)

For these types of surgeries, surgeons with 5 or more years of experience used prophylactic AEDs less frequently than those who practiced less than 5 years (54.0% vs. 70.0%, $P = 0.0094$). ABNS certified neurosurgeons also used AEDs less often (55.7% vs. 68.1%, $P = 0.0487$). Surgeons who tended to specialize in brain tumor craniotomies were more likely to use prophylactic AEDs for awake craniotomies: Brain tumor surgeries comprised 28.5 ± 25.2% of cases performed by neurosurgeons who were more likely to administer AEDs, compared to 20.8 ± 19.6% of operations performed by surgeons using AEDs less often ($P = 0.0074$). Otherwise, no significant difference was noted in the use of AEDs with regards to the type of practice, degree of specialization, whether or not epilepsy surgery was part of the regular practice, AANS/CNS Joint Tumor Section membership, and total number of surgeries.

Benign extra-axial tumors ($n = 366$ replies)

Surgeons who have been in practice for 5 or more years indicated that they prophylactically administer AEDs more often than their colleagues who have practiced less than 5 years (58.7% vs. 42.9%, $P = 0.0052$). ABNS certified neurosurgeons used AEDs significantly more than non-ABNS certified surgeons (57.8% vs. 43.7%, $P = 0.0149$). The use of AEDs in this patients' group also depended on the type of neurosurgeon's practice: patients treated in small and large private practice groups were somewhat more likely to receive AED prophylaxis than patients of neurosurgeons working in academic centers (59.3% and 67.8%, vs. 45.8%, $P = 0.0055$). The degree of specialization was a significant variable as well: 58.4% of patients treated by "general" neurosurgeons received AEDs compared to 46.9% of patients treated in subspecialty practices ($P = 0.0313$). A significant difference in the use of AEDs was also noted between the surgeons who performed epilepsy surgery as part of their regular practice and those who did it sporadically (34.8% vs. 59.9%, $P < 0.0001$). The total number of surgeries, membership in the AANS/CNS Joint Tumor Section, and their percentage of brain tumor cases were not statistically significant variables in the benign extra-axial tumor group.

Multivariate analysis

On multivariate analysis, the number of years in practice was associated with higher likelihood of using prophylactic AEDs for patients with extra-axial brain tumors (odds ratio 1.18 (1.04–1.38), $P = 0.04$) and with a lower likelihood for awake craniotomy with functional mapping (odds ratio 0.69 (0.57–0.83), $P < 0.001$). The number of years in practice was also associated with a lower likelihood of using AED prophylaxis amongst ABNS certified neurosurgeons in the following groups: intra-axial low-grade tumors with transcortical approach (odds ratio 0.69 (0.51–0.93), $P = 0.01$), intra-axial high-grade tumors with transcortical approach (odds ratio 0.68 (0.49–0.93), $P = 0.02$) and brain metastases (odds ratio 0.66 (0.50–0.893), $P = 0.005$). Multivariate analysis also demonstrated that in the benign extra-axial group, neurosurgeons who performed epilepsy surgery as part of their routine surgical practice used AEDs significantly less frequently than their non-epilepsy colleagues (odds ratio 0.39 (0.23–0.64), $P = 0.0002$).

Management of AEDs by neurosurgeons

An additional six survey questions addressed issues related to the choice and management of prophylactic AEDs. Due to a data collection error, the responses from question 16, which asked whether a neurology referral was routinely obtained, were lost and therefore were not available for analysis. The majority of respondents start prophylactic AEDs before or at the time of surgery (288/299, 96.3%). A wide range of practices were utilized for deciding when to stop prophylactic AED administration, but the majority of respondents indicated that they would stop prophylactic AEDs within 6 weeks of surgery (172/299, 57.5%, see Table 2). In the event of a peri-operative seizure, however, the majority of respondents would continue AEDs for at least 3 months (190/323, 58.8%) and fewer (69/323, 21.4%) indicated that they would defer to a neurologist for this decision. The majority of responding neurosurgeons also indicated that they managed and adjusted AED levels (where applicable) on their own (204/248, 82.3%). Only 54 of 301 (17.9%) indicated that they would obtain an EEG prior to stopping prophylactic AEDs. Nearly all respondents (298/310, 96.1%) used phenytoin as their agent of choice for seizure prophylaxis.

Table 2. AED administration practices

Timing of AED discontinuation	Number (percentage)
After 1 dose	3 (1.0%)
At hospital discharge	11 (3.7%)
After 1 week	55 (18.4%)
After 2 weeks	25 (8.4%)
After 4–6 weeks	78 (26.1%)
After 3 months	72 (24.1%)
After 6 months	26 (8.7%)
After 1 year	8 (2.7%)
Other	21 (7.0%)

Discussion

Limitations of this study

The major limitation of our study is that it is solely based on the retrospective, self-reported data. One problem stemming from this study design is that the respondents might be influenced by the pressure to follow some published guidelines, and provide the answers they believe the authors of the study would want them to provide. The results of our study, however, showed that the opinion of the majority of the responding neurosurgeons was contrary to what the AAN guidelines recommended. Another limitation is that the respondents simply could have poor recall of their own practice patterns [13,14]. The third limitation lies in the fact that only 15.5% of the targeted practitioners responded, which could by itself create some bias. Nonetheless, 386 replies represent an opinion of the significant cohort of surgeons and exceeds the number of respondents in the previous surveys. Finally, although almost half of the respondents were from various academic centers, we believe this should not create a bias as, in our opinion, a large proportion of brain tumors are treated in larger centers which have access to more technologically advanced surgical tools.

Prophylactic anticonvulsants in brain tumors: what does the survey reflect?

One of the main recommendations of the American Association of Neurology guidelines on anticonvulsant prophylaxis in brain tumor patients without prior history of seizures was that the routine use of AEDs should be discouraged. Moreover, the guidelines emphasized the negative sequelae of AEDs interactions with cytotoxic drugs and steroids seen in 20–40% of brain tumor patients. This is particularly the case with the new small molecule drugs used for targeted therapy of gliomas. The metabolism of many of these agents is profoundly affected by the administration of hepatic enzyme-inducing anti-epileptics (e.g. phenytoin, carbamazepine), and separate arms (on- or off-enzyme inducing AEDs) must be created for evaluating these agents in clinical trials. Although the evidence does not support the routine use of AEDs in this population, the reality, as demonstrated by our survey, shows that the absolute majority of neurosurgeons still prefer to administer AEDs to brain tumor patients.

Somewhat similar results were published by Brouwers et al, who surveyed 122 practitioners, the majority of whom were neurologists and oncologists, and only 22.1% were neurosurgeons [15]. Interestingly, 70% of mostly non-surgical practitioners indicated that perioperative anticonvulsant prophylaxis either ''always'' or ''sometimes'' indicated. If, however, not only surgical patients were considered, 80% of respondents noted that less than 25% of their clinical cases involved the use of AEDs. Therefore there is a considerable difference between the principles summarized in the AAN guidelines and the realities of brain tumor patient management by neurosurgeons and other practitioners.

Our impression is that neurosurgeons seem to remain more enthusiastic about perioperative AED use in brain tumor patients than other practitioners. One explanation for this observation is that there is a desire to avoid possible negative sequelae of seizures in post-operative period, such as a hypothetically increased risk of bleeding immediately after surgery, neurologic decline, or even seizure-associated death. A peri-operative seizure could have quality of life implications as well, as many states restrict driving privileges for months, even up to 1 year, after a single seizure.

Before the survey, we hypothesized that the number of years in practice of ABNS certified neurosurgeons would be associated with higher likelihood of using prophylactic AEDs and specialization in epilepsy surgery with lower likelihood of AED prophylaxis. Although most of the studies discouraging the prophylactic use of AEDs have been done in the past 20 years, their results have never been presented systematically and the attention of the practitioners treating brain tumor patients has not been drawn to this issue until the publication of the American Association of Neurology guidelines 4 years ago and the publicity it earned. This could likely affect the training and philosophy of a substantial number of neurosurgeons. The results of the survey, however, showed that the older neurosurgeons were, in a sense, more in line with the AAN recommendations using AED prophylaxis less frequently in all patients groups except extraaxial brain tumors. As for the epilepsy specialization, our results showed the initial hypothesis to be true only in relation to patients with extraaxial brain tumors as well. In all other patients groups the approach of epilepsy neurosurgeons to AED prophylaxis was no different from the rest of neurosurgeons.

Another observation from our survey is that the decisions on the use of AEDs in brain tumor patients are generally not influenced by the membership in the AANS/CNS Joint Section on Tumors, and the size and type of practice. This finding probably reflects the fact that none of the neurosurgical organizations to date have produced any formal guidelines for seizure prophylaxis in general for neurosurgical patients, and in brain tumor patients in particular. The only exception to this observation are guidelines for the use of prophylactic anticonvulsants after traumatic brain injury published by the Brain Trauma Foundation with the American Association of Neurological Surgeons, Joint Section on Neurotrauma and Critical Care [16]. One of the standards of these guidelines is that routine use of AEDs after one week following brain injury is not recommended for prevention of late seizures. These recommendations, however, cannot be directly extrapolated to brain tumor patients.

Finally, it is important to emphasize that variations in practice can be based on the needs, morbidity rates and variations in consumer preferences for different outcomes in specific patient groups [8]. Therefore, in some situations, the decision to follow or deviate from the guideline is not explicitly right or wrong [15,17]. Nonetheless, we believe introduction of the prophylactic AED use guidelines is important in bringing scientific evidence

to the area of standardization and optimization of patient care.

What are the future directions?

The main shortcomings of previous studies of prophylactic use of AEDs in brain tumor patients are the retrospective nature of most of them and the relatively small number of patients. Another important issue is that only three AEDs have been evaluated: phenytoin, carbamazepine, and valproic acid. New generation AEDs, such as levetiracetam (Keppra™), although widely used, have not been evaluated in clinical trials. Additional larger prospective studies with inclusion of newer drugs are, therefore, warranted.

Another area of interest might be the consideration of various subgroups of brain tumor patients. For instance, some types of brain tumors (e.g. located in the vicinity of the motor strip, melanomas, and hemorrhagic lesions) were shown to be more prone to manifest with seizures [7,18–21]. Thus, evaluation of possible benefits (or lack thereof) in studies with appropriate patient stratification may also be necessary in creation of future guidelines.

In summary, the results of our survey demonstrated that routine use of AED prophylaxis in patients with brain tumors undergoing neurosurgical procedures remains the prevailing practice pattern among members of the AANS despite the lack of convincing evidence in support of such approach. Further investigation in this area will be necessary before a comprehensive neurosurgical set of guidelines on prophylactic use of AEDs in patients with brain tumors can be created.

Acknowledgement

The authors would like to acknowledge the technical assistance provided by Kathleen T. Craig and Heather Monroe of the American Association of Neurological Surgeons.

References

1. Boarini DJ, Beck DW, VanGilder JC: Postoperative prophylactic anticonvulsant therapy in cerebral gliomas. Neurosurgery 16: 290–292, 1985
2. Cohen N, Strauss G, Lew R, Silver D, Recht L: Should prophylactic anticonvulsants be administered to patients with newly-diagnosed cerebral metastases? A retrospective analysis. J Clin Oncol 6: 1621–1624, 1988
3. Forsyth PA, Weaver S, Fulton D, Brasher PM, Sutherland G, Stewart D, Hagen NA, Barnes P, Cairncross JG, DeAngelis LM: Prophylactic anticonvulsants in patients with brain tumour. Can J Neurol Sci 30: 106–112, 2003
4. Franceschetti S, Binelli S, Casazza M, Lodrini S, Panzica F, Pluchino F, Solero CL, Avanzini G: Influence of surgery and antiepileptic drugs on seizures symptomatic of cerebral tumours. Acta Neurochir 103: 47–51, 1990
5. Glantz MJ, Cole BF, Friedberg MH, Lathi E, Choy H, Furie K, Akerley W, Wahlberg L, Lekos A, Louis S: A randomized, blinded, placebo-controlled trial of divalproex sodium prophylaxis in adults with newly diagnosed brain tumors. Neurology 46: 985–991, 1996
6. Mahaley MS Jr, Dudka L: The role of anticonvulsant medications in the management of patients with anaplastic gliomas. Surg Neurol 16: 399–401, 1981
7. Moots PL, Maciunas RJ, Eisert DR, Parker RA, Laporte K, Abou-Khalil B: The course of seizure disorders in patients with malignant gliomas. Arch Neurol 52: 717–724, 1995
8. De Santis A, Villani R, Sinisi M, Stocchetti N, Perucca E: Add-on phenytoin fails to prevent early seizures after surgery for supratentorial brain tumors: a randomized controlled study. Epilepsia 43: 175–182, 2002
9. Foy PM, Chadwick DW, Rajgopalan N, Johnson AL, Shaw MD: Do prophylactic anticonvulsant drugs alter the pattern of seizures after craniotomy? J Neurol Neurosurg Psychiatry 55: 753–757, 1992
10. Lee ST, Lui TN, Chang CN, Cheng WC, Wang DJ, Heimburger RF, Lin CG: Prophylactic anticonvulsants for prevention of immediate and early postcraniotomy seizures. Surg Neurol 31: 361–364, 1989
11. Temkin NR: Prophylactic Anticonvulsants After Neurosurgery. Epilepsy Curr 2: 105–107, 2002
12. Glantz MJ, Cole BF, Forsyth PA, Recht LD, Wen PY, Chamberlain MC, Grossman SA, Cairncross JG: Practice parameter: anticonvulsant prophylaxis in patients with newly diagnosed brain tumors. Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 54: 1886–1893, 2000
13. Adams AS, Soumerai SB, Lomas J, Ross-Degnan D: Evidence of self-report bias in assessing adherence to guidelines. Int J Qual Health Care 11: 187–192, 1999, Review
14. Eccles M, Ford GA, Duggan S, Steen N: Are postal questionnaire surveys of reported activity valid? An exploration using general practitioner management of hypertension in older people. Br J Gen Pract 49: 35–38, 1999
15. Brouwers MC, Chambers A, Perry J: Neuro-oncology Disease Site Group. Can surveying practitioners about their practices help identify priority clinical practice guideline topics? BMC Health Serv Res 3: 23, 2003
16. The Brain Trauma Foundation, The American Association of Neurological Surgeons. The Joint Section on Neurotrauma and Critical Care: Role of antiseizure prophylaxis following head injury. J Neurotrauma 17: 549–553, 2000, Review
17. Council National Health and Medical Research: A guide to the development, implementation and evaluation of clinical practice guidelines. (Edited by: AusInfo). Australia 1999
18. Berger MS, Ghatan S, Haglund MM, Dobbins J, Ojemann GA: Low-grade gliomas associated with intractable epilepsy: seizure outcome utilizing electrocorticography during tumor resection. J Neurosurg 79: 62–69, 1993
19. Deutschman CS, Haines SJ: Anticonvulsant prophylaxis in neurological surgery. Neurosurgery 17: 510–517, 1985
20. Gilles FH, Sobel E, Leviton A, Hedley-Whyte ET, Tavare CJ, Adelman LS, Sobel RA. Epidemiology of seizures in children with brain tumors. The Childhood Brain Tumor Consortium. J Neurooncol 12: 53–68, 1992
21. Glantz MJ, Recht L: Epilepsy in the cancer patient. In: Vinken PJ, Bruyn GW (eds) Neuro-oncology. Part III. Neurological disorders in systemic cancer. Handbook of clinival neurology, Vol 69. Elsevier Publishing, Amsterdam 1997: pp 9–18

Address for offprints: Michael A. Vogelbaum M.D., Ph.D., The Cleveland Clinic Brain Tumor Institute, 9500 Euclid Ave, ND-40, Cleveland, OH 44195, Tel.: 216-445-5522; Fax: 216-444-2682; E-mail: vogelbm@neus.ccf.org