

# A retrospective two-center study of antiepileptic prophylaxis in patients with surgically treated high-grade gliomas

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## Abstract

**Background:** The effectiveness of antiepileptic prophylaxis in patients with newly diagnosed high-grade glioma is debated. Craniotomy, surgical manipulation and bleeding are believed to favor the onset of seizures and, therefore, perioperative antiepileptic drugs (AEDs) are generally used. Nevertheless, evidence to initiate preoperative AED prophylaxis are weak. **Aim:** Aim of this paper was to evaluate the need for AED prophylaxis in surgically-treated malignant glioma patients without history of seizures. **Materials and Methods:** We conducted a retrospective, two-center cohort study to assess the effectiveness of preoperative AED prophylaxis. Patients were divided in two groups: one with AED preoperative administration and the other without. Because of its non-hepatic metabolism, levetiracetam (LEV) was chosen. Logistic regression models were used to investigate the odds ratio for each group. The explanatory variables included the treatment received, sex, age, and site of lesion. The outcome measure of successful LEV prophylaxis was seizure vs. no seizure post-operatively, at three and six months after surgery. **Results:** Our results showed that LEV prophylaxis was not a significant predictor of seizure occurrence, although the regression coefficient indicated a slight reduction in seizure risk following LEV administration. Patient's age was a significant predictor of seizure occurrence. Younger patients had a higher risk of seizure in the six months post-surgery. **Conclusions:** We conclude that AEDs prophylaxis does not provide a substantial benefit to surgically treated high-grade glioma patients and should not be administered routinely. Further investigations are required to detect subgroups of patients at higher risk of developing seizures in order to selectively administer AED.

**Key words:** Antiepileptic Drugs, glioma, levetiracetam, prophylaxis, seizures, surgery

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## Introduction

Approximately 40% of high-grade glioma patients present with seizures at onset.<sup>[1]</sup> Location of the glioma plays a role in epileptogenesis, and temporal and parietal lobes are more often associated with seizures than other areas of the brain. Patient age and previous cancer treatment also contribute to epileptogenesis.<sup>[2]</sup> If initiation of antiepileptic treatment is justified after a first and single seizure in patients with brain tumors, it is uncertain if AED prophylaxis should be prescribed

to brain tumor patients who have never had a seizure. Moreover, the majority of high-grade glioma patients are treated surgically with a resection or biopsy, and the appearance of post-operative seizures, both early and delayed is a predictable event. Surgical manipulation and bleeding usually generate inflammation and edema that are believed to favor the onset of seizures.<sup>[3,4]</sup> Furthermore, all glioblastoma (GBM) patients and a large percentage of grade III glioma patients are eventually treated with anticancer agents and steroids and, thus, the risk of potential drug interactions influences the choice of AED.

Existing brain damage from previous surgery or radiotherapy increases the risk of developing side effects from AEDs. A consensus statement from the Quality Standards Subcommittee of the American Academy of Neurology<sup>[2]</sup> recommends not to use AEDs routinely as prophylaxis in patients with brain tumors and to withdraw these drugs in the first week after surgery if patients have not had a seizure. The few analyses that have been conducted on AED prophylaxis in patients undergoing craniotomy,<sup>[3-8]</sup> were confounded by the fact that different kinds of brain tumors (gliomas, metastasis, and meningiomas) were evaluated together, multiple AEDs were employed, and patients with preoperative seizures were included in the study. In clinical practice, many physicians continue to administer AEDs pre- and post-operatively with the aim of avoiding seizures.

In the current study, we evaluated the need for AED prophylaxis in surgically-treated high-grade glioma patients with no history of seizures. With a follow-up of at least six months, we also observed the difference in the appearance of delayed post-operative seizures and long-term adverse effects between AED-treated patients and a control group. Because of its demonstrated efficacy, tolerability and non-hepatic metabolism, we chose Levetiracetam (LEV) as the first-line AED in the treated group.

## Materials and Methods

### Study protocol

The retrospective, multicenter cohort study was conducted by the Division of Neurosurgery of the Hospitals of Turin and the Division of Neurosurgery of the Civil Hospital of Alessandria. The study period was January 2009 through December 2010.

In total, 143 patients harboring high-grade gliomas were consecutively operated on in the Neurosurgical Divisions of Turin and Alessandria. Consistent with routine clinical practice, patients in the Turin neurosurgical department were treated with preoperative AED prophylaxis, but Alessandria patients were not. Patients who met the inclusion criteria for the study

were divided into two cohorts. In Group A (Turin Hospital; LEV prophylaxis), patients received LEV as a prophylactic AED preoperatively, following the schedule described below. In Group B (Alessandria Hospital; control), only patients who did not receive prophylaxis were included.

Patients' demographic data, tumor location, preoperative Karnofsky Performance Scale (KPS) score, post-operative complications and histology were analyzed and differences in frequency according to patient group were calculated.

### Inclusion criteria

Patients with newly-diagnosed, untreated, supratentorial high-grade gliomas without seizures were included in the study. Patients had no history of seizures or suspected anamnesis. Only patients with complete or subtotal resection of their tumor were selected. Complete resection was defined when the contrast-enhanced tumor was no more visible on post-contrast MR or CT performed the day after surgery.

### Exclusion criteria

Patients with multicentric lesions or gliomas involving the midline, basal ganglia, cerebellum or brain stem were excluded from the study. Also, patients who experienced seizures as a symptom of disease or received treatment or prophylaxis with AED were excluded, as were those with a KPS score of less than 60.

### Levetiracetam schedule

LEV was administered three to five days before surgery. The daily administration was 1 g (500 mg twice a day). In all cases, blood samples were drawn before surgery in order to evaluate the LEV plasma level. We performed surgery after achieving LEV serum levels above 15 ug/ml. We underline that the routine sample of the plasma level of LEV is actually our practice although it is not required for this kind of AED. The post-operative LEV plasma concentration was also assessed. LEV was administrated after surgery according to the same schedule (500 mg twice a day) in the absence of seizures. The treatment was continued up to six months after surgery. If seizures occurred post-operatively, the LEV dose was increased to 2 g/day (1000 mg twice a day) or another AED was used.

### Neuropathology

The histopathological criteria were established according to the World Health Organization 2007 diagnostic consensus criteria.<sup>[9]</sup>

### Post-operative evaluation and follow-up

The post-operative protocol was the same for all the patients and consisted of radiotherapy and concomitant temozolomide. The seizure-free interval was first

assessed post-operatively, then within 30 days after surgery and then checked at three and six months. The immediate post-operative control is made by the surgeon, while the late post-operative control (within one month from the operation) is conducted by the neurooncologist. Then, the neurooncologist follow-up the patients at fixed intervals and collect the neurological status, as well as all the physical and neurological changes on standardized charts.

### Statistical analysis

The outcome measure of successful LEV prophylaxis was seizure vs. no seizure at three and six months after surgery. Logistic regression models were used to investigate the odds ratio for groups A and B. The explanatory variables included the treatment received, sex, age, and site of lesion. Significant ( $P < 0.05$ ) variables in the multiple regression analysis were found by the backward elimination method. Results are presented as odds ratios and 95% CIs.

### Results

A total of 91 patients were included in the study (52 males and 39 females). Forty-three patients were included in Group A and 48 patients in Group B. The Table 1 summarizes the characteristics of the whole series of 143 patients based

**Table 1: Summary of the whole series of 143 patients operated on for intracranial gliomas in both centers during the study period**

Inclusion and exclusion criteria	Enrolled (%)	Excluded (%)
No seizures at diagnosis	91 (63.6)	
Seizures at diagnosis		28 (19.5)
Multicentric, posterior fossa, corpus callosum, basal ganglia		24 (16.7)
KPS<60		17 (11.8)*
Already on AED prophylaxis		12 (8.3)*
Total number of patients (143)	91 (63.6)	52 (36.6)

KPS - Karnofsky performance scale, AED - Antiepileptic drugs patients are subdivided in those who matched the inclusion criteria and those who were excluded. (\*) The patients in these two groups have to be considered as subcategories as these subjects could also belong to the first two groups (i.e., patients with multicentric glioma and KPS<60)

**Table 2: Demographic details and characteristics**

Features of patients and gliomas	Group A (N=43)	Group B (N=48)	P value
Mean age (SD)	59.47 (12.0)	63.9 (11.8)	$t_{(89)}=1.77$ ; $P=0.08$
Sex (N): Male/female (ratio)	28/15 (1.87)	24/24 (1.0)	$\chi^2=2.12$ ; $P=0.15$
Preoperative KPS score>80	40 (43.9%)	44 (48.3%)	$U=1029.5$ ; $P=0.98$
Postoperative complications	1 (1%)	2 (2.1%)	
N° of GBM	27 (29.6%)	31 (34%)	$\chi^2=0.032$ ; $P=0.86$
N° of grade III anaplastic	16 (17.5%)	17 (18.6%)	
Site of tumor			
Frontal	20 (21.9%)	21 (23%)	$\chi^2=1.064$ ; $P=0.79$
Occipital	3 (3.2%)	2 (2.1%)	
Parietal	5 (5.4%)	4 (4.3%)	
Temporal	15 (16.4%)	21 (23%)	

SD - Standard deviation,  $t$  -  $T$ -test value,  $\chi^2$  - Chi-squared coefficient,  $U$  - Mann-Whitney coefficient, GBM - Glioblastoma, KPS - Karnofsky performance scale

on the selection's criteria. The participants' ages ranged from 27 to 76 years; the mean age of the global sample was 61.8 years (SD = 12.03); the mean age of Group A was 59.47 years (SD = 12.0) and the mean age of Group B was 63.9 years (SD = 11.8). None of the patients enrolled in the analysis showed drug or psychotropic drug abuse and none suffered from other major neurologic diseases.

The most frequent symptoms at diagnosis were behavioural changes followed by hemiparesis and language or praxis disturbances. Headache, related to intracranial hypertension, was present in approximately 25% of patients. Preoperative KPS score was over 80 in the majority of patients in both groups. Table 2 shows inter-group differences in distributions of age, sex, preoperative KPS score, post-operative complications, and histology.

Surgery was performed in all cases by means of craniotomy and resection of the contrast-enhanced mass. Post-operatively, urgent craniotomy was performed because of tumor cavity infarction in three patients (3.2%). All of these patients had a residual tumor left following surgery (deep position or tumor strictly adherent to vessels) and all three patients completely recovered after reoperation.

All patients harbored high-grade gliomas, including 58 GBM and 33 anaplastic astrocytomas (AA). Post-operative LEV levels ranged between 15 and 40 ug/ml. Side effects were rare, with only one case of vertigo reported.

### Group A

#### Early post-operative period and thirty days after surgery

A 54-year-old male harboring a temporal GBM experienced seizures. A right temporal lobectomy was performed. The LEV dosage was increased to 2000 mg/day with complete control of seizures.

#### Three-month follow-up

Five patients experienced seizures (2 temporal GBM, 2 frontal GBM, and 1 parietal AA). First, the dose of

LEV was increased to 2000 mg/day. Complete seizure control was achieved in three cases. In two patients, we observed a poor response and treatment was changed to a multi-drug approach (carbamazepine 1200 mg/day and sodium valproate 1000 mg/day) with subsequent stabilization of the seizures.

**Six-month follow-up**

Two patients experienced seizures. Partial control was achieved by increasing LEV to 2000 mg/day. After dose adjustment, one patient showed severe ataxia. LEV was stopped and changed over to sodium valproate 1200 mg/day with partial seizure control and ataxia improvement.

**Group B**

**Early post-operative period and thirty days after surgery**

No seizures were observed in the perioperative period.

**Three-month follow-up**

Three patients developed focal seizures. No response to LEV 2000 mg/day was observed among these patients, and treatment was switched to oxcarbazepine 900 mg/day with complete seizure control.

**Six-month follow-up**

Six patients experienced seizures. Complete control was obtained with LEV 2000 mg/day in three cases. However, good control was not achieved in three patients and treatment was switched to oxcarbazepine 900 mg/day with partial control of seizures.

**Data analysis**

The rate of seizure occurrence within one month after surgery was globally very low (2.3% in Group A, while no patients in Group B had seizures). Since the rate of seizures in the perioperative period was extremely low, we could not include these data in the statistical analysis. At three months, the cumulative rates of seizure were 13.9% in Group A and 6.2% in Group B. At six months, the cumulative rates of seizure were 18.5% in Group A and 18.75% in Group B. All the patients that developed seizures in the follow-up period were different from those who presented seizures in the perioperative period. Table 3 reports the frequency of seizures at the post-operative and follow-up period.

We tested the effect of LEV prophylaxis on the occurrence of seizures within six months post-surgery by fitting the data to a logistic regression model, which determines the effect of an independent variable to predict membership of one or other of the two dependent variable categories (occurrence vs. no occurrence). Treatment was the independent variable, i.e. the effect of the treatment was included as predictor of the occurrence of seizure; age and gender were entered as covariates,

which are variables that may be related to the event under investigation (i.e. the occurrence of seizure). LEV prophylaxis was not a significant predictor of seizure occurrence ( $b = -0.140, P = 0.818, OR = 0.869$ ), although the regression coefficient indicated a slight reduction in seizure risk following LEV administration. Patients age was a significant predictor of seizure occurrence ( $b = -0.049, P = 0.042, OR = 0.952$ ). Younger patients had a higher risk of seizure in the six months post-surgery; for each 10-year increase in age, a patient's odds of seizure decreased by 39% ( $OR = 0.613$ ). The regression coefficient suggested a lower risk of seizures in males, but the effect of gender was not significant ( $b = -0.842, P = 0.159, OR = 0.431$ ). Two-way interactions between treatment, age, and gender were further tested and found to be non-significant. The data are displayed in Table 4.

**Discussion**

The frequency of seizures in patients harboring supratentorial brain tumors is as high as 40%<sup>[2,10]</sup> and surgery itself is believed to add a relevant risk of perioperative seizures.<sup>[11]</sup> Several clinicians and neurosurgeons use AEDs as prophylaxis in order to prevent seizures,<sup>[12]</sup> despite potential adverse effects and drug interactions. Moreover, high-grade glioma patients are frequently exposed to neurosurgery, radiotherapy and chemotherapy and, therefore, they present particular risks to the initiation and maintenance of additional therapy.

First-generation AEDs such as phenytoin, carbamazepine, valproic acid and phenobarbital have been used to treat seizures in patients with glioma. These agents are known to cause a higher incidence of side effects,

**Table 3: Occurrence of post-operative seizures at early post-operative period (until 30 days after surgery), three months and six months**

Occurrence of seizures	Group A (LEV prophylaxis) (%)	Group B (no prophylaxis) (%)
Early post-operative	1 (1.1)	0
Three months	5 (5.4)	3 (3.2)
Six months	2 (2.1)	6 (6.5)
Total	8 (8.7)	9 (9.8)

LEV - Levetiracetam

**Table 4: Logistic regression analysis of risk of seizure in surgically treated high-grade gliomas patients**

Predictor	b	SE	Wald $\chi^2$	P	OR
Intercept	1.782	1.534	1.35	0.245	-
LEV prophylaxis (0=no; 1=yes)	-0.140	0.606	0.053	0.818	0.869
Age (years)	-0.049	0.024	4.121	0.042	0.952
Gender (0=F; 1=M)	-0.842	0.599	1.981	0.159	0.431

b - Logistic coefficient, SE - Standard error, OR - Odds ratio, LEV - Levetiracetam

especially phenytoin, whose most feared side effect is Stevens-Johnson syndrome.<sup>[13-15]</sup> Moreover, phenytoin, like many other first generation AEDs, undergoes oxidative metabolism through the hepatic cytochrome P450 (CYP) system; phenytoin is an enzyme-inducing AED and can potentially increase the clearance of chemotherapeutic agents metabolized through the CYP system including antineoplastic drugs used for glioma therapy.<sup>[16,17]</sup> Interactions between antiepileptic drugs and antineoplastic agents may lead to insufficient control of the tumor or epilepsy or to toxic effects of one or both of the agents. Drug interactions are usually pharmacokinetic-based and affect drug uptake, metabolism in the liver, or elimination of the drug.

Enzyme-inducing AEDs decrease the effectiveness of corticosteroids and several chemotherapeutic agents. Oberndorfer and colleagues<sup>[18]</sup> conducted a retrospective study of patients with GBM who were given adjuvant chemotherapy (most received lomustine), and found that overall survival of patients who received an enzyme-inducing antiepileptic drug (most received carbamazepine) was significantly shorter than for those who received a non-enzyme-inducing antiepileptic drug (most received valproic acid; 10.8 vs. 13.9 months, respectively). More recently, different authors demonstrated how LEV and valproic acid can increase the activity of and the response to chemotherapy.<sup>[19,20]</sup> On the other hand, many chemotherapeutic agents induce coenzymes of the CYP pathway and change the plasma concentration of AEDs.<sup>[16]</sup>

New antiepileptic drugs such as gabapentin, LEV, and pregabalin do not interact with other agents, as they do not influence the CYP or other metabolic pathways. To date, few side effects associated with LEV have been reported, including dizziness, disturbed mood, fatigue and somnolence, in several series<sup>[18,21-24]</sup> of patients with brain tumors who received antineoplastic agents simultaneously. Therefore, LEV has been increasingly used as an AED for brain tumor patients over the past decade, particularly in patients undergoing early post-operative chemotherapy.<sup>[18,25]</sup>

The precise mechanisms by which LEV exerts its antiepileptic effect is unknown, but it is thought to stimulate synaptic vesicle protein 2A (SV2A), which inhibits neurotransmitter release. In animal models, LEV did not inhibit single seizures induced by maximal stimulation with electrical current or different chemoconvulsants and showed only minimal activity in submaximal stimulation and in threshold tests.<sup>[26]</sup> Protection was observed, however, against secondarily generalized activity from focal seizures induced by pilocarpine and kainic acid, two chemoconvulsants that induce seizures that mimic some features of human complex partial seizures with secondary generalization,

and in the kindling model in rats, another model mimicking partial seizures.

The issue of AED prophylaxis in brain tumor patients has been extensively discussed in the last two decades and AED prophylaxis has been proposed for some indications.<sup>[27]</sup> The major evidences were revealed when authors started performing meta-analyses of several works on this topic. In 2001, Temkin<sup>[28]</sup> analyzed six prospective, controlled trials that involved patients undergoing neurosurgery for different diagnoses (tumors, trauma) and found that AED prophylaxis (predominantly phenytoin) reduced seizures in the early post-operative period. This work had the great limitation of comparing patients belonging to populations with very different risks of seizure (trauma and tumor patients) and the author admitted the need for studies on homogeneous categories of patients. A large meta-analysis performed by Glantz *et al.*,<sup>[2]</sup> evaluated 12 studies involving brain tumor patients (either randomized controlled or cohort studies), but no demonstration of the efficacy of prophylaxis was disclosed. The authors failed to solve the matter because the study models were not completely suitable. As a matter of fact, they were retrospective studies or did not have placebo-controlled patients. Moreover, the pooling of patients harboring different kind of tumors with different risks of seizure (meningiomas, metastasis, gliomas) made those results less robust. In 2002, De Santis,<sup>[29]</sup> published a prospective work that evaluated the usefulness of prophylaxis in the specific category of surgically-treated supratentorial tumor patients. They found that phenytoin was not able to prevent seizures, either as monotherapy or in cases where an AED was already administered. This study had the important limitation of including subjects already suffering from seizures preoperatively and patients previously treated with AED. In order to focus on patients without seizures at onset and assemble a larger population of patients, Sirven<sup>[30]</sup> performed a meta-analysis of five studies that dealt with only seizure-free patients (a total of 403 subjects), but only three included patients undergoing craniotomies. All these studies had the advantage of being prospective and placebo-controlled, but patients with different kinds of tumors were included and, in some studies, multiple AEDs were employed. Moreover, all the AEDs were last generation drugs. Four of these studies could not demonstrate the efficacy of AED prophylaxis and surgery did not influence the risk of seizure onset.

The most evident limitation of the current study is its retrospective structure, but performing a prospective trial on this topic would have been troublesome in relation to the number of patients to enrol and the expected high mortality rate of these patients. Still,

although the use of cohorts from different hospitals could have introduced some bias, it is worth noting that these two Institutions share the same surgical and post-operative protocol, that is the indications for surgery are similar, as well as the methods of following-up patients. In this work, we investigated the occurrence of post-operative seizure in a large sample of patients, revealing no significant effect of LEV prophylaxis on seizure occurrence. Our results provide additional insight into the cost/benefit analysis of LEV prophylaxis, although further studies on larger samples are needed to accurately detect a small effect.

Our findings indicate that the prophylactic administration of LEV does not provide a substantial benefit to surgically-treated high-grade glioma patients. This may be due to the low dose of LEV employed for prophylactic treatment, compared to that used in acute treatment, owing to the need to limit side effects for a long-term administration. In fact, a review of the data in the literature on the possible role of prophylactic antiepileptic treatment with traditional agents (phenytoin, phenobarbital, carbamazepine) for early post-operative seizures shows that the main reason for therapeutic failure is subtherapeutic serum concentrations of the drugs. In some studies, serum concentration monitoring was not conducted, making it impossible to establish whether the drug was ineffective or not.<sup>[25,28]</sup> In the current study, post-operative LEV plasma concentrations were within the therapeutic range in all the patients.

## Conclusions

Antiepileptic prophylaxis in patients with intracranial tumors is still a matter of debate. In this specific category of patients with high-grade gliomas undergoing craniotomy, AED prophylaxis should not be administered routinely. Further investigations detecting subgroups of patients at higher risk of developing seizures post-operatively (i.e. younger patients) are welcome in order to selectively administer AED prophylaxis.

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