Efficacy and Safety of Oxcarbazepine as Monotherapy for Prevention of Epileptic Seizures in Patients With Supratentorial Brain Tumors: A Prospective Multicentric Study

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Objectives: Brain tumor–related epilepsy management poses significant challenge in clinical practice. Healthcare providers must tailor treatment based on each patient's unique circumstances. Different antiepileptic drugs can be used, including oxcarbazepine. Several studies show this drug's efficacy and safety in brain tumor–related epilepsy.

Methods: Observational, prospective study, monitoring the efficacy and safety of the drug oxcarbazepine in the prevention of epileptic seizures, included adult patients of both sexes with a supratentorial tumor and a risk of epileptic seizures after neurosurgery.

Results: The study included 153 hospitalized patients. The percentages of amplified waves, sharp waves, and spike waves decreased in the second and third compared with the first visit. Significantly lower percentages of sharp waves ($P = 0.028$) on the second compared with the first measurement and spike waves ($P = 0.002$) on the third compared with the first measurement were determined. Deterioration from normal to low hemoglobin concentration was observed in 40 (26%) patients at the second visit and 17 (12%) at the third visit, compared with the first visit. However, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration values did not change significantly during the 6 months of follow-up. A transient drop in the number of thrombocytes was observed on the second visit. Adverse reactions to the drug were mild. Therapeutic adherence was low, as measured by the Morisky Medication Adherence Scale (MMAS-4).

Conclusions: The drug oxcarbazepine has shown good efficacy and safety in the prevention of epileptic attacks after neurosurgery in patients with supratentorial tumors. Additional education of patients on the importance of taking regular therapy is crucial.

Key Words: brain tumor–related epilepsy, oxcarbazepine, efficacy, safety

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Epilepsy is a prevalent manifestation in individuals afflicted with brain tumors often called brain tumor–related epilepsy (BTRE), frequently serving as an initial indication of an underlying pathology. BTRE refers to seizures occurring in the context of brain tumors. These tumors can be primary (originating within the brain) or metastatic (spreading from other sites). The incidence of BTRE varies widely, ranging from 35% to 90% across different histological types and locations.[1] Seizures may manifest as focal (partial) or generalized, depending on the tumor's location and impact on neural networks. Patients with gliomas located in the temporal, insular, or frontal regions experience a higher incidence of epilepsy, with oligodendrogliomas showing a particularly close relationship to preoperative seizures. The pathophysiological mechanisms underlying epilepsy in glioma patients are complex and involve numerous factors, although our understanding of this process remains limited.[2,3] The management of seizures associated with these tumors poses a significant challenge, underscoring the importance of utilizing effective antiepileptic drugs in such cases. In brain tumor patients, it is crucial to attain lasting control over epileptic seizures. Uncontrolled seizures can significantly impact the quality of life in these patients. Many drugs can be used for the treatment of BTRE.[4,5]

Among these drugs, oxcarbazepine has emerged as a noteworthy option due to its proven efficacy and tolerability in addressing seizures linked to brain tumors. Oxcarbazepine is an antiepileptic drug commonly used to manage various seizure disorders, primarily partial seizures with or without secondarily generalized tonic-clonic seizures. Oxcarbazepine blocks voltage-gated sodium channels, which leads to stabilization of neuronal membranes and reduction of abnormal electrical activity.[4] Oxcarbazepine has been investigated as monotherapy in patients with BTRE to assess its efficacy and impact on quality of life. In a prospective observational study, 25 patients with BTRE were given oxcarbazepine monotherapy

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Data are available from the corresponding author upon reasonable request.

The authors confirm that they have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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The study involved human participants and was approved by the Agency for Medicinal Products and Medical Devices of Bosnia and Herzegovina (08-07.5-2192-1/22 from 24.05.2022.) and by the ethical review boards of participating institutions.

The Helsinki Declaration from 1975 and its amendments from 1983 were followed in all procedures. Before any procedure started, each participant signed an informed consent form.

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due to uncontrolled seizures or side effects. After 12 months of follow-up, significant improvements were seen in seizure freedom rates and mood. The study suggests oxcarbazepine may effectively control seizures and improve mood in patients with BTRE, but caution is advised when administering it during radiotherapy.[5]

In summary, oxcarbazepine holds promise as a valuable option for managing seizures in patients with BTRE.[6] However, healthcare providers must tailor treatment based on each patient's unique circumstances. Further research and clinical experience will continue to refine our understanding of oxcarbazepine's role in this complex interplay between brain tumors and epilepsy.

The aim of this study was to evaluate the efficacy, safety, and therapy adherence to oxcarbazepine therapy used in the prevention of epileptic seizures after neurosurgical procedures in patients with supratentorial tumors.

MATERIALS AND METHODS

Study Population and Procedures

This was an observational, prospective study monitoring the efficacy and safety of the drug oxcarbazepine in the prevention of epileptic seizures that included adult patients of both sexes with a supratentorial tumor and a risk of epileptic seizures after neurosurgery. The study was performed from July 2022 to September 2023, at 3 investigational sites in Bosnia and Herzegovina (Clinical Center University of Sarajevo, University Clinical Center Tuzla, and Cantonal Hospital Zenica). Exclusion criteria were hypersensitivity to the components of the drug oxcarbazepine, positive history of angioneurotic edema, severe liver failure, moderate and severe renal insufficiency (glomerular filtration rate <30 mL/min), use of hormonal contraceptives, bone marrow depression, heart rhythm disorders (atrioventricular block), hyponatremia (<134 mEq/L), and pregnancy or nursing. Withdrawal criteria were deterioration of the underlying disease that requires therapy discontinuation, development of serious adverse events that require discontinuation of therapy, occurrence of pregnancy, and withdrawal of informed consent by the patient.

Oxcarbazepine (Exmal tablets; Bosnalijek d.d., Sarajevo, Bosnia and Herzegovina) was introduced for 6 months according to the summary of product characteristics dosing schedule[7] supported by data available from other clinical trials in this indication. Therapy started within 7 days before the surgical procedure. On the first day, patient received 300 mg once a day; the second day, 300 mg twice a day; and the third day, 600 mg twice a day. After that, a maintenance dose of 600 mg twice a day was applied for the next 6 months.

At the first visit, oxcarbazepine therapy was included within 7 days before surgery, and demographic data were collected with blood pressure, heart rate, date of tumor diagnosis, presence and type of preoperative epileptic attacks, laboratory results, and electroencephalogram (EEG). The second visit was performed 1 month, and the third visit was performed 6 months after discharge of the patient from the hospital. At both visits, adverse events, therapy adherence by 4-item Morisky Medication Adherence Scale (MMAS-4),[8] blood pressure, heart rate, and laboratory parameters were recorded. The safety of drug administration was evaluated through the monitoring of the incidence of possible adverse drug events by the investigator with the assessment of the connection between the administration of the drug and the occurrence of an adverse reaction.

The clinical trial was approved by the agency for medicinal products and medical devices of Bosnia and Herzegovina (08-07.5-2192-1/22 from 24.05.2022) and by the ethical review boards of participating institutions. The Helsinki Declaration from 1975 and its amendments from 1983 were followed in all procedures. Before any procedure started, each participant signed an informed consent form.

Statistical Analysis

The usual descriptive statistics (absolute and relative numbers) were applied. Checking whether the data distribution is normal and whether there are outliers was carried out by looking at frequency histograms of individual measurements and Q-Q and box-plot graphs, analyzing z values for skewness and kurtosis, and the Kolmogorov-Smirnov test. Only the data on the number of erythrocytes had a normal distribution without outliers in all 3 measured points. After it was determined that the assumption of sphericity was met (by using Mauchly test), the number of erythrocytes at 3 time points was analyzed using the 1-way analysis of variance test for repeated measurements, which determined that there was no difference between the groups and no post hoc analysis was performed. Differences in 3 time points for other numerical variables were analyzed with the Friedman test, after which a comparison of pairs was made using the Wilcoxon signed-rank test with the application of the Bonferroni correction, where $P < 0.0167$ was accepted as a statistically significant difference. Cochran Q test was used to compare the presence of spike-and-wave in the 3 measurements. Before the analysis, the sample size was estimated. Adequate sample size was determined for all analyses ($n > 4$ and $n * k > 24$), and Cochran Q test was used. When a statistically significant difference was determined by Cochran Q test, Dunn post hoc test was performed with Bonferroni correction. $P < 0.05$ was accepted as a statistically significant difference, except in the case of tests where the Bonferroni correction was applied. Analyses were performed by using SPSS program version 23.0 (IBM Corp, Armonk, NY).

RESULTS

The study included 153 hospitalized patients with a supratentorial tumor undergoing neurosurgery (Table 1). The percentages of

TABLE 1. Baseline Characteristics of Patients Included Into the Study

Parameters	All Patients (n = 153)
Age,* y	57 (48–67)
Sex,† male	84 (55)
Smoking†	61 (40)
Alcohol consumption†	15 (10)
BMI,† kg/m^2	
<20	8 (5)
20–25	98 (64)
25.1–30	35 (23)
>30	9 (6)
Unknown	3 (2)
Physical activity†	131 (86)
Diabetes†	19 (12)
Preoperative epileptic attacks†	40 (26)
Generalized	34 (22)
Partial	6 (4)

*Data are presented as median (interquartile range).

†Data are presented as absolute numbers (percentage concerning the total number of respondents).

BMI, body mass index.

TABLE 2. Values of EEG Parameters on 3 Measurements

Parameters	First Visit (n = 153)	Second Visit, After 1 mo (n = 152)	Third Visit, After 6 mo (n = 146)	*P*
Amplified waves	19 (12)	17 (11)	12 (8)	.595
Sharp waves	18 (12)	8 (5)	12 (8)	**.034**
Spike waves	20 (13)	10 (7)	7 (5)	**.002**

Data are presented as absolute numbers (percentage concerning the total number of respondents). Statistically significant differences at the level of $P < 0.05$ are bolded.

amplified waves, sharp waves, and spike waves decreased in the second and third compared with the first visit. Using Cochran *Q* test, a statistically significant difference between the time points was determined regarding the number of sharp waves and spike waves (Table 2). By using Dunn post hoc test with the application of Bonferroni correction, significantly lower percentages of sharp waves ($P = 0.028$) on the second compared with the first measurement and spike waves ($P = 0.002$) on the third compared with the first measurement were determined. There were no significant differences between other measurement points.

By comparing the parameters on 3 measurements using the Friedman test, a difference in the hemoglobin concentration and number of thrombocytes between different time points was observed (Table 3). A drop in the hemoglobin concentration was observed in 89 subjects at the second compared with the first measurement, which was a statistically significant difference, $z = -3.20$, $P = 0.001$ ($P < 0.0167$ was considered statistically significant with the application of the Bonferroni correction). At the third compared with the first measurement, 78 subjects had a drop in the hemoglobin concentration, which was a statistically significant difference, $z = -3.04$, $P = 0.002$. There was no statistically significant difference in the hemoglobin concentration at the third compared with the second measurement, $z = 0.66$, $P = 0.510$. When considering reference values for women (119–157 g/L) and men (138–175 g/L), at the first visit 40% of patients had low hemoglobin, and this percentage increased to 51% at the second and 53% at the third visit. When compared with the first visit, deterioration from normal to low concentrations of hemoglobin was observed in 40 (26%) patients at the second visit and 17 (12%) at the third visit (Fig. 1). However, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) values did not change significantly during the 6 months of follow-up.

A drop in the number of thrombocytes was observed in 87 subjects at the second compared with the first measurement, which was a statistically significant difference, $z = -2.66$, $P = 0.008$. At the third compared with the second measurement, 84 subjects had an increase in the number of thrombocytes, which was not a statistically significant difference after Bonferroni correction, $z = 2.11$, $P = 0.035$. There was no statistically significant difference in the number of thrombocytes at the third compared with the first measurement, $z = 0.24$, $P = 0.812$. For the other monitored parameters, including the mineral analysis, no difference was observed between the 3 measurements (Table 3).

Two deaths not related to the use of the drug were recorded. Deaths were due to the consequences of the underlying disease and occurred in the period between the second and third measurements. Adverse reactions to the drug were recorded in 7 patients (Table 4).

TABLE 3. Laboratory Parameters' Values for 3 Measurements

Parameters	First Visit (n = 153)	Second Visit, After 1 mo (n = 152)	Third Visit, After 6 mo (n = 146)	*P*
Systolic blood pressure,* mm Hg	130.0 (120.0–140.0)	130.0 (120.0–150.0)	130.0 (120.0–150.0)	.922
Diastolic blood pressure,* mm Hg	80.0 (70.0–90.0)	80.0 (70.0–90.0)	80.0 (75.0–90.0)	.614
Heart rate*	80.0 (68.0–94.0)	80.0 (68.0–99.3)	80.0 (71.3–95.0)	.770
Erythrocytes,† 10^{12}/L	4.1 ± 1.0	4.1 ± 1.0	4.1 ± 1.0	.892
Hemoglobin,* g/L	**136.0 (121.0–144.0)**	**129.0 (118.8–139.0)**	**127.5 (116.3–140.0)**	**.025**
Hematocrit,* L/L	0.4 (0.4–0.5)	0.4 (0.4–0.5)	0.4 (0.3–0.5)	.797
Leukocytes,*10^9/L	8.6 (6.3–11.2)	7.8 (6.0–11.0)	8.6 (6.5–11.9)	.127
Thrombocytes,* 10^9/L	**278.0 (219.0–346.0)**	**240.0 (196.8–314.3)**	**276.0 (212.0–360.0)**	**.026**
MCV,* fL	90.0 (85.6–95.0)	89.8 (84.7–95.0)	92.5 (87.1–96.2)	.070
MCH,* pg	29.0 (27.3–30.7)	28.6 (26.9–30.5)	29.2 (27.4–30.9)	.554
MCHC,* g/dL	34.0 (32.7–35.5)	33.5 (32.3–34.9)	34.1 (32.5–35.6)	.115
MPV,* fL	9.2 (8.1–10.0)	8.9 (8.0–10.0)	9.3 (8.3–10.2)	.062
RDW,* %	13.4 (12.4–14.7)	13.5 (12.3–14.9)	13.6 (12.2–14.5)	.976
Glucose,* mmol/L	6.5 (4.9–9.1)	7.0 (5.1–9.7)	7.1 (5.0–9.2)	.192
AST,* U/L	26.0 (14.7–35.0)	27.5 (17.0–39.0)	24.0 (13.0–34.8)	.883
ALT,* U/L	25.0 (17.0–37.0)	29.5 (17.8–37.3)	26.0 (16.0–36.0)	.963
Potassium,* mmol/L	4.1 (3.6–4.6)	4.1 (3.7–4.7)	4.1 (3.5–4.8)	.766
Sodium,* mmol/L	140.0 (137.0–144.0)	139.0 (136.0–144.0)	141.5 (136.0–145.0)	.060
Calcium,* mmol/L	2.4 (2.1–2.6)	2.2 (1.8–2.5)	2.3 (1.6–2.6)	.108
Urea,* mmol/L	5.4 (3.8–7.1)	5.3 (3.4–6.6)	5.1 (3.4–6.9)	.694
Creatinine,* μmol/L	75.0 (56.0–92.0)	77.5 (62.0–90.0)	78.0 (59.0–93.0)	.532

*Data are presented as median (interquartile range).

†Data are presented as mean value (±SD).

ALT, alanine aminotransferase; AST, aspartate aminotransferase; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MPV, mean platelet volume; RDW, red cell distribution width. Statistically significant differences at the level of $P < 0.05$ are bolded.

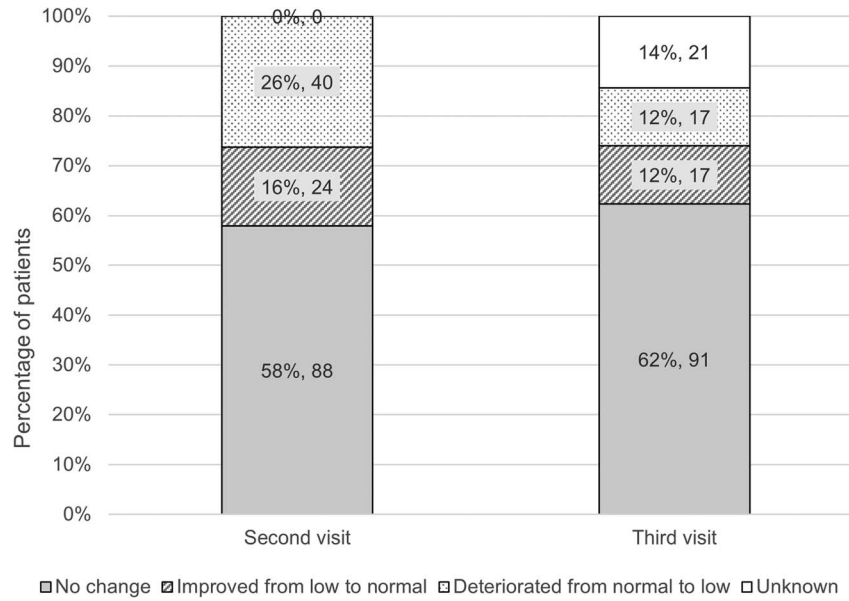

FIGURE 1. Changes in hemoglobin concentration on the second (after 1 month) and third visit (after 6 months) compared with the first visit. Labels represent percentage concerning the total number of respondents and absolute numbers.

The Morisky score as a measure of therapeutic adherence was constant during the entire study with a median value of 4.0 (interquartile range, 3.0–4.0), which is in the range of low adherence.

DISCUSSION

This study found good efficacy and safety but low therapy adherence to oxcarbazepine therapy used in the prevention of epileptic seizures after neurosurgical procedures in patients with supratentorial tumors.

In the literature, there is a limited number of studies of BTRE. In the study by Dao Trong et al, the drug library included 20 Food and Drug Administration–approved antiepileptic drugs that have been selected based on literature reviews and clinical practice. The decision to include these drugs was largely influenced by evidence from non–tumor-related epilepsy, with limited data available for treating tumor-related epilepsies.[9] However, levetiracetam, phenytoin, and pregabalin are generally recommended as first-line treatments for tumor-associated epilepsy by some authors. If monotherapy with these drugs is not successful, carbamazepine, lacosamide, oxcarbazepine, topiramate, perampanel, and valproate are commonly used as alternative or adjunct therapies.[9–11] Dao Trong et al found a unique characteristic of oxcarbazepine, which has been identified as having antiproliferative effects on isocitrate dehydrogenase mutant glioma stem cells. This effect is attributed to its proapoptotic properties. These findings have the potential to pave the way for incorporating oxcarbazepine, an antiepileptic drug, into existing chemotherapy regimens for individuals with epileptogenic isocitrate dehydrogenase mutant gliomas.[9] In a study of first-line monotherapy of oxcarbazepine, authors found that this drug had efficacy in patients with BTRE regarding control of seizures and mood improvement.[6]

The efficacy of oxcarbazepine was monitored by EEG. A significantly lower percentage of sharp waves on the second visit 1 month after therapy start, compared with the first visit, was observed. However, on the third visit, 6 months after therapy start, percentage of sharp waves increased again but was not statistically significant compared with both the first and the second visit. Kim et al found that oxcarbazepine monotherapy was not associated with a significant change in background EEG spectral power or coherence.[12] Utilizing the latest EEG mapping technology and targeted tumor therapies, a holistic multidisciplinary management strategy should be implemented to enhance the quality of life, as well as long-term oncological and seizure outcomes for individuals afflicted with epilepsy associated with brain tumors.[13]

TABLE 4. Recorded Adverse Drug Reactions With the Listed MedDRA Version 26.1 System Organ Class (SOC) Classifications

	Second Visit, After 1 mo (n = 152)	Third Visit, After 6 mo (n = 146)
No. of patients with adverse reactions	5 (3.3)	2 (1.4)
Rash—SOC skin and subcutaneous tissue disorders	1	0
Skin changes in the form of redness and palmoplantar rash—SOC skin and subcutaneous tissue disorders	1	0
Dizziness—SOC nervous system disorders	2	1
Stomach pain—SOC gastrointestinal disorders	1	0
Nausea—SOC gastrointestinal disorders	0	1

Data are presented as absolute numbers (percentage concerning the total number of respondents) or only absolute numbers.

As it is well-documented, hematological side effects are associated with antiepileptic drugs. These medications have been linked to a range of adverse reactions including thrombocytopenia, leukopenia, neutropenia, pancytopenia, pure red cell aplasia, aplastic anemia, macrocytosis, megaloblastic anemia, and bone marrow depression.[14,15] The most common side effects of oxcarbazepine are skin rash, headache, dizziness, nausea, sedation, and hyponatremia.[16] Oxcarbazepine is one of the relatively safe antiepileptic drugs.[17] In our study, the safety of oxcarbazepine therapy was evaluated by laboratory parameters analysis and adverse reaction recording. Hemoglobin concentration significantly decreased 1 and 6 months after therapy start. However, MCV, MCH, and MCHC values did not change significantly during the same period. A transient decrease in the number of thrombocytes was observed, whereas a drop in the number of thrombocytes was observed at the second visit; it increased at the third visit and was similar to the first visit. There have been a limited number of studies evaluating the link between carbamazepine and thrombocytopenia, and even fewer studies are available for oxcarbazepine. Thrombocytopenia seems to be a rare side effect of oxcarbazepine, with more commonly reported side effects being dizziness, fatigue, memory issues, and headaches. The proposed course of action for treating antiepileptic drug–induced thrombocytopenia is to stop the medication and closely monitor platelet levels.[18] Special consideration should be given to pediatric patients. A retrospective study of pediatric patient medical files of 184 individuals diagnosed with epilepsy or a movement disorder who were receiving treatment solely with oxcarbazepine showed that oxcarbazepine-induced leukopenia is not rare and may result in pancytopenia. Regular monitoring for abnormal complete blood count profiles is needed in patients treated with oxcarbazepine.[19]

Oxcarbazepine together with levetiracetam, valproic acid, lamotrigine, gabapentin, and topiramate is the most commonly used antiepileptic drug in patients with brain tumors.[20] Oxcarbazepine is found to be one of the safest and most effective antiepileptic drugs for the prevention of seizures of BTRE. Maschio et al found that in individuals experiencing seizures associated with brain metastases, oxcarbazepine is effective in reducing seizure frequency, with minimal side effects and no apparent impact on life expectancy, independent of systemic treatment.[6] We have shown that oxcarbazepine usage had little and mild adverse drug reactions.

The future use of antiepileptic drugs in patients with brain tumors can give possible better outcomes for patients. Valproic acid, oxcarbazepine, lacosamide, lamotrigine, and levetiracetam have demonstrated promising potential in aiding the treatment of various cancers. Although antiepileptic drugs may serve as a viable option for adjuvant cancer therapy, further research is necessary to fully evaluate their effectiveness in clinical trials for cancer treatment.[21]

Limitations

This study had several limitations; first, there was a small number of included patients. Also, additional efficacy and safety evaluations should be included. A larger, comparative, blinded, randomized study should be performed to confirm the findings of our study.

CONCLUSION

The drug oxcarbazepine has shown good efficacy and safety in the prevention of epileptic attacks after neurosurgery in patients with supratentorial tumors. Additional education of patients on the importance of taking regular therapy is crucial, considering that low adherence to therapy was determined in this study. Additional research with a larger sample is needed to confirm the results of our study.

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