Effect of Pre-Operative Antiepileptic Drugs on Post-Operative Seizure Incidence and Recovery in Brain Tumor Resections: Levetiracetam vs. Valproate

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Abstract

Background

Postoperative seizures resulting from brain tumor resections negatively impact patient recovery. Among currently widely used antiepileptic drugs (AEDs) for seizure prophylaxis, are Levetiracetam and Valproate, however there seem to be varied efficacy and safety profiles. This study contrasts the effectiveness of Levetiracetam to Valproate in reducing post operative seizures and evaluating their influence on cognitive recovery and liver function.

Objective

The aim is to compare postoperative seizure incidence between patients taking either Levetiracetam or Valproate preoperatively, and also to assess functional recovery through cognitive and neurologic endpoints as well as drug related side effects, particularly liver enzyme levels.

Method

This is a prospective, randomized, controlled trial of 100 brain tumor resection patients, who were randomly assigned to Levetiracetam, or Valproate groups. Seizure occurrence postoperatively was followed at 24 hours, 7 days, 1 month, and 3 months in these patients. The functional recovery was assessed using the modified Rankin Scale (mRS), and cognitive function was assessed using the Montreal Cognitive Assessment (MoCA). The serum liver enzyme levels are ALT, AST and GGT were monitored at specific intervals to see changes in liver function. T tests and chi square tests were used to compare between the two groups.

Results:

Seizure incidence was lower consistently in the Levetiracetam group at all time points, but did not achieve statistical significance. MoCA indicated significant improvement in cognitive recovery in the Levetiracetam group at 24 h, 7 days, 1 and 3 months after surgery; ($p < 0.05$). Functional recovery scores (mRS) were not significantly different between the two groups. Nevertheless, liver enzyme values were significantly higher ($p < 0.05$) postoperatively in the Valproate group than that of Levetiracetam Group.

Conclusion:

Levetiracetam did not result in significantly less (compared with Valproate) postoperative seizure incidence, however, it was associated with significantly better cognitive recovery and a safer liver function profile. For patients at risk of seizures for brain tumor resection, particularly those concerned about liver toxicity, levetiracetam may be a better choice.

Introduction

Management of the risk of postoperative seizures associated with brain tumor treatment is complex and may negatively impact recovery (Medikonda et al., 2020). Tumor resection in patients is concerned about seizure control because post-operative seizures are associated with poor outcome (Rudà et al., 2020). This is commonly utilised with antiepileptic drugs (AEDs) of which Levetiracetam and Valproate are the most used (Pathak et al, 2023). A recent study has compared their safety and efficacy and some find Levetiracetam to be better tolerated (Faghihjouibari et al., 2023). However, Valproate remains often used widely, especially in patients with behavioral complications (Gilliam et al., 2023). The hepatotoxicity observed with Valproate has been of concern (Ganesh et al., 2023). Studies like those of Watanabe et al (2022) point to Levetiracetam, especially in combination with sodium channel blockers, having better postoperative seizure control (Watanabe et al., 2022). In addition, results from several randomised trials need to be taken into account in assessing the long term effect of AED use in this patient group (Jenkinson et al. 2020). Finally, the AED to be selected should be personalized based on both efficacy and side effects in the individual (Rahman et al., 2022).

The aim of this study was to compare seizure rates in patients who received levetiracetam versus valproate as preoperative antiepileptic drug in brain tumor resections. The study also sought to assess functional recovery post surgery through patient reported outcomes and cognitive, and neurological function. The research also attempted to analyze and document possible drug related side effects, like fatigue, and changes in liver enzyme levels linked with each medication.

Study design

A prospective, randomized controlled trial was designed to assess the effect of preoperative antiepileptic drugs (AEDs) on postoperative seizure incidence and recovery in patients who undergo brain tumor resections. Before surgery, patients were randomly assigned to receive levetiracetam or valproate. A computer generated randomization sequence was used to ensure equal distribution between the two groups and randomization was performed. Blinding was applied at the level of outcome assessors to minimize bias, though both patients and surgical teams were aware of the assigned treatment due to the nature of drug administration.

Sample Size Calculation:
The sample size was calculated to detect a clinically significant reduction in post-operative seizure incidence between the two groups. Based on previous studies, it was estimated that levetiracetam would result in a 20% reduction in post-operative seizure rates compared to valproate. Assuming a baseline post-operative seizure incidence of 30% in the valproate group and a reduction to 10% in the levetiracetam group, the study aimed to achieve 80% power with a two-sided significance level (alpha) of 0.05. Using these parameters, a minimum of 45 patients per group was required. To account for potential dropouts and incomplete data, the final sample size was set at 50

patients in each group, for a total of 100 patients. It was determined that this sample size would be large enough to have sufficient power to detect meaningful difference between the two treatment groups. The basic protocol included standardized protocols for the management of the patient including timing and dose of AEDs administered. We collected baseline data on demographic parameters, tumor characteristics and preexisting neurological status prior to surgery in order to control for possible confounding variables. The use of adjunct therapies was recorded, and the two groups of patients received similar surgical procedures. Patients were monitored post operatively for presence of seizure activity, and functional recovery assessed multiple time points at validated patient reported outcome measures for cognitive and neurological function. It also traced any drug related side effects, with a focus on fatigue and changes in liver enzymes. Short and long term outcomes were evaluated using data collected over a predetermined follow up period. Primary and secondary outcomes were compared between the two groups with statistical analyses pre-specified.

Patient selection criteria

The patient selection criteria for this study were determined for adult patients undergoing brain tumor resections who were considered at risk for developing post-operative seizures. All of the patients were over age 18 and had a proven diagnosis of a brain tumor which necessitated surgical resection. The study included primary and metastatic brain tumors. The study was conducted in patients who had not in the past suffered seizures due to the brain tumor; the study was to examine the prophylactic use of antiepileptic drugs (AEDs).

In addition, patients with a history of epilepsy or pre-existing seizure disorders unrelated to the brain tumor, which might confound an evaluation of post-operative seizure risk, were excluded. To avoid possible interaction effects, patients were also excluded who were currently taking any AEDs for conditions unrelated to tumors. They also added people with severe liver and kidney problems, which could impact on how drugs are metabolized and make them more likely to have adverse effects. Additionally, patients with hypersensitivity (or known allergies) to either levetiracetam or valproate were excluded from participation.

Because of the potential teratogenic effects of the study medications, pregnant or breastfeeding women were not eligible for the study. Patients with serious cognitive or psychiatric disease that might prevent them from giving informed consent or completing patient reported outcome measures were also excluded. All patients gave written informed consent before enrollment; patients were thoroughly explained the aims, risks, and procedures of study.

Recruitment from multiple participating centres took place from those patients who met the inclusion criteria and none of the exclusion criteria. Each patient was subject to a full preoperative evaluation consisting of demographic data collection, detailed medical history, neurological examination, and confirmation of tumor features by imaging studies. The rigorous selection process in this study made the patient population homogeneous such that results from this study would specifically address the effects of preoperative AED use on postoperative seizure incidence and recovery.

Study group allocation (Levetiracetam group vs. Valproate group)

Patients who met the inclusion criteria were randomly assigned to one of two groups: the Treatment group (the Levetiracetam group or the Valproate group). To avoid biased distribution, group allocation was performed using a computer generated randomization sequence. The randomization was centralized and stratified by key variables like age, tumor type and tumor location in order to minimize confounding by any measure of outcome.

In the Levetiracetam group, levetiracetam was used as the antiepileptic drug (AED) pre-operatively and in the Valproate group, valproate was administered. Standardized dosing protocols for each AED were adhered to in the pre-operative administration as based on current clinical guidelines. In both groups, the selected AED was given at least 48 hours before surgery but at drug levels within the plasma before surgery happened. Dosing was adjusted based on patient weight and renal function, as required, and was monitored regularly throughout the peri-operative period.

The study design did not allow for crossover between groups, and patients continued on the assigned AED throughout the post-operative period unless a severe adverse reaction occurred, in which case the medication would be discontinued according to protocol. Post-operatively, patients in both groups received standard post-surgical care, with the only difference in treatment being the assigned AED. The surgical teams and other healthcare providers were aware of the group allocation, but the outcome assessors who evaluated seizure incidence, functional recovery, and side effects were blinded to the treatment groups to reduce bias in reporting.

Patients were monitored for seizure activity, and assessments were conducted at pre-specified intervals post-surgery to measure both short- and long-term outcomes. Any changes in medication, adverse events, or withdrawals from the study were documented. The random allocation process, along with strict adherence to dosing protocols and blinding of outcome assessors, ensured that the comparison between levetiracetam and valproate was robust and methodologically sound.

Surgical procedure (brain tumor resections)

The surgical procedure involved standard brain tumor resection techniques, tailored to the specific tumor location and type for each patient. All surgeries were performed by experienced neurosurgeons following established protocols to ensure consistent care across the study. The aim was complete or maximal safe tumor resection, with intraoperative monitoring used to minimize damage to surrounding healthy brain tissue. Post-operatively, patients were closely monitored for neurological changes and complications. Surgical records, including tumor size, resection extent, and operative duration, were documented for all patients.

Post-operative seizure monitoring

Post-operative seizure monitoring was conducted rigorously to assess the incidence and frequency of seizures in both the Levetiracetam and Valproate groups. All patients were transferred postoperatively to the recovery unit and then to a neuro intensive care unit where continuous electrocephenalographic (EEG) data was collected for the first 48 hours to detect subclinical and clinical seizure activity. Trained medical staff also evaluated patients for overt seizure symptoms, such as focal or generalized seizures, during a patient's hospital stay and during follow up visits. Clinical evaluation tools were used by standardized seizure assessments at specific times postoperatively (24 hrs, 1 wk, 1 mo, 3 mo) both at time of hospital discharge and 3 and 6 mo out. Any observed seizures were delineated into type, duration, severity, and other relevant data were recorded in a central database. Patients and caregivers were also instructed to report any seizure like events that occurred after discharge and follow up appointments were completed including detailed questioning to capture any missed episodes. Further EEGs were done in suspected cases of seizure activity to ensure the diagnosis. Blinding to the patient's treatment group ensured unbiased reporting of all the seizure events subjected to review by the neurologists.

Functional recovery assessment (patient reported outcomes)

Based on the postoperative seizure monitoring schedule, functional recovery was assessed using patient reported outcomes at 24 hours, 7 days, 1 month and 3 months post surgery. The assessments focused on both cognitive and neurological recovery, using two primary tools: we used the Montreal Cognitive Assessment (MoCA) and the modified Rankin Scale (mRS).

Montreal Cognitive Assessment (MoCA):

To assess domains of cognitive function including memory, attention, language, visuospatial ability and executive functioning, the MoCA was administered. This 30 point scale includes short term memory recall, serial subtraction, sentence repetition, and drawing a clock, tests of visuospatial skill. A normal score is something that scores 26 or above, and as you go down in numbers it is considered to be a different level of cognitive impairment. Cognitive function was repeatedly assessed regarding the change at pre-defined time points to see if the cognitive function changed following the surgery using MoCA assessments. The Levetiracetam and Valproate groups were compared on patients' scores over time to see if cognitive ability was improving or deteriorating among those in each group.

Modified Rankin Scale (mRS):

The degree of disability or dependence in daily activities was assessed by the use of the mRS. It is on the scale from 0 to 6, where 0 means no symptoms and 6, death. Scores, ranging from 1 to 5, reflect from minimal disability (1) to severe disability (requiring constant care) (5). The mRS was used to see how physically independent and how they are recovering functionally after each of the follow ups of patients. Motor function, speech and ability to carry out normal daily activities without help were focused for neurological recovery using the mRS.

Cognitive recovery was assessed at each time point (24 hours, 7 days, 1 month, 3 months) using MoCA; and functional independence and overall neurological recovery using mRS. Compared with the two treatment groups, the first documented any significant cognitive or neurological decline. Together with patient reported outcomes, these tools gave a detailed picture of the recovery process and enabled comprehensive analysis of differences between patients on levetiracetam and patients on valproate.

Side effects monitoring

The potential adverse effects from levetiracetam and valproate were also monitored systematically during this study. Subsequently patients were closely observed for both subjective symptoms (such as fatigue) and objective biochemical changes (liver enzyme alterations) as both drugs are known to produce these side effects.

Fatigue Assessment:

A standardized fatigue severity scale was used to ask patients to report their levels of fatigue, with intensity and impact of fatigue in daily activities being reported. Other functional recovery evaluations and fatigue assessments were performed at 24 hours, 7 days, 1 month and 3 months post surgery respectively. Fatigue was rated mild to severe by patients, and these reports were painstakingly documented to compare prevalance and severity across the two groups. Somewhat longer than 3 months, any significant or prolonged episodes of fatigue were investigated to determine if such fatigue could be accounted for by postoperative complications or infections.

Liver Enzyme Monitoring:

All patients were monitored closely for potential hepatotoxic effects of valproate during the course of the study. Serum levels of three liver enzymes alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT) were measured with blood samples collected at baseline (pre operatively), and 7 days, 1 month, and 3 months post surgery. As potential side effects, any significant elevations in these enzymes, above the upper limit of normal, were documented. Further investigations were made if an elevated liver enzyme was found, with the need to continue the AED reevaluated.

Other Side Effects:

The common side effects discovered, in addition to fatigue and liver enzymes monitoring, included dizziness, nausea, headache and mood changes as they occurred with both levetiracetam and valproate. In the study database, new or worsened symptoms were recorded if patients reported them during the follow-up visits and were encouraged to report them. The study’s medical team, blind to treatment groups,

reviewed any adverse reactions. Serious adverse events were reported as per study protocol and adjustments were made to medication dosages when appropriate.

As part of this study, we aimed to not only compare the efficacy (i.e., reduction of seizure frequency) of levetiracetam vs. valproate in reducing post-operative seizures but also to examine their safety profiles to allow a comprehensive evaluation of the risk-benefit balance of each drug, by monitoring these side effects.

Data collection and data management

The study was designed carefully so that data were collected and managed to remain accurate, consistent, and confidential. Data from all relevant patient information such as demographic data, preoperative assessments, operative details, post operative outcome, and side effects were collected using the case report forms (CRF) devised for this study specifically. Trained research staff at each participating center completed these forms.

Shocks were applied at multiple time points: baseline (pre-operatively), 24 hours, 7 days, 1 month, and 3 months post-operatively during the assessment of seizures, functional recovery and side effects. Systematic clinical data (e.g. seizure incidence, mRS and MoCA) and laboratory results (liver enzymes) were entered into an electronic data management system for each patient. The patient information was on this system, which was password protected and meeting data protection regulations so that the system would be safe.

All data entered within the system passed routine checks from an independent data monitoring team to ensure data quality and minimize errors. All discrepancies and missing information were called up immediately with the concerned center. Also we reviewed the data periodically for consistency and complete. Regularly backups were taken, in case there would be a technical issue and the data would be lost. Confidentiality of patients was maintained throughout the study. Identifying information of the patients was separated out from clinical data to guarantee privacy with each patient assigned a unique identification number. The data were restricted to access only by authorized study personnel and all data handling procedures conformed to ethical standards and local regulatory rules. All follow up visits were completed and the final dataset was locked with a final quality check and analysis undertaken. In this cleaned and validated dataset, statistical analyses were performed on this dataset to analyze the outcomes between the Levetiracetam and Valproate groups. Adhering to these data collection and management protocols allowed the study to be reliable and accurate in the results.

Statistical analysis methods

Simple statistical methods for continuous and categorical data were employed for statistical analysis, comparing the Levetiracetam and Valproate outcomes. All analyses were performed using standard statistical software, and a significance level (alpha) of 0.05 was set for all tests.

Continuous data such as seizure frequency, MoCA scores, and liver enzyme levels (ALT, AST, GGT) were summarized using means and standard deviations. To

compare these continuous variables between the two groups, independent sample t-tests were used, assuming normal distribution of the data. For variables that were not normally distributed, non-parametric tests, specifically the Mann-Whitney U test, were applied.

Categorical data, such as the presence or absence of post-operative seizures, drug-related side effects, and mRS scores (grouped into levels of functional independence), were summarized using frequencies and percentages. Chi-square tests were used to compare these categorical variables between the two groups. In cases where expected cell counts were small, Fisher's exact test was used as an alternative to ensure the validity of the comparison.

All results were presented with corresponding p-values and 95% confidence intervals to quantify the level of statistical significance and the precision of the estimates. These methods allowed for a clear comparison of the key outcomes, including post-operative seizure incidence, functional recovery, and side effects, between the Levetiracetam and Valproate groups.

Results

Table 1: Statistical Comparisons Between Levetiracetam and Valproate Groups for Demographics and Pre-Operative Parameters

Parameter	Levetiracetam group (n=50)	Valproate group (n=50)	p-value
Age (years)	49.72 ± 9.65	52.26 ± 11.79	0.203
Gender (Male/Female)	30 (60.0%) / 20 (40.0%)	28 (56.0%) / 22 (44.0%)	0.689
Pre-Op Neurological Status (Normal/Impaired)	36 (72.0%) / 14 (28.0%)	33 (66.0%) / 17 (34.0%)	0.529
Pre-Op MoCA	25.60 ± 2.11	24.54 ± 2.92	0.051
Pre-Op ALT (U/L)	30.36 ± 4.68	32.46 ± 6.06	0.064
Pre-Op AST (U/L)	25.24 ± 4.26	27.16 ± 5.28	0.086
Pre-Op GGT (U/L)	34.82 ± 6.85	39.14 ± 8.56	0.004

There were no statistically significant differences between the two groups for most of the parameters, including age, gender distribution, pre-operative neurological status, and pre-operative cognitive function (MoCA). However, a borderline non-significant difference was observed in Pre-Op MoCA scores ($p = 0.051$), with the Levetiracetam group showing slightly higher scores. Pre-operative liver enzyme levels (ALT and AST) were also comparable between the groups, though GGT levels were significantly higher in the Valproate group ($p = 0.004$).

Table 2: Statistical Comparisons Between Levetiracetam and Valproate Groups for Post-Operative Seizure Occurrence

Parameter	Levetiracetam group (n=50)	Valproate group (n=50)	p-value
Seizures 24hr	3 (6.0%)	3 (6.0%)	1.000

Seizures 7d	4 (8.0%)	7 (14.0%)	0.523
Seizures 1m	6 (12.0%)	12 (24.0%)	0.193
Seizures 3m	7 (14.0%)	15 (30.0%)	0.091

- Fisher's exact test was used for Seizures at 24 hours due to low expected values, while the chi-square test was used for Seizures at 7 days, 1 month, and 3 months.
- A p-value less than 0.05 was considered statistically significant.

Although the Valproate group exhibited a higher frequency of post-operative seizures at all time points, the differences between the Levetiracetam and Valproate groups were not statistically significant.

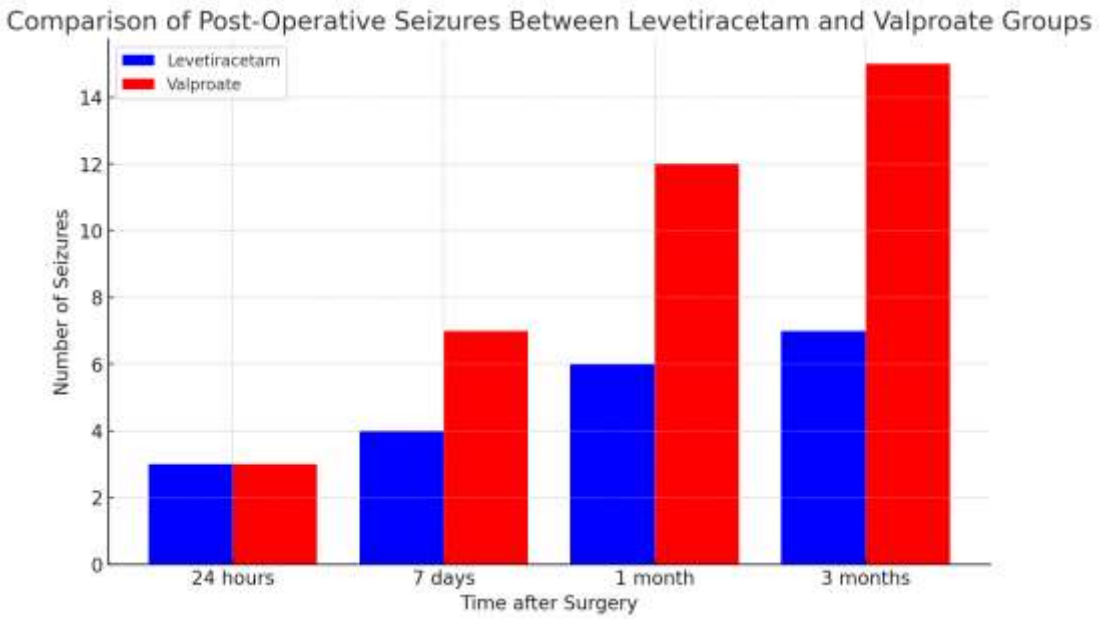

Figure 1: Comparison of Post-Operative Seizures Between Levetiracetam and Valproate Groups

Table 3: Statistical Comparisons Between Levetiracetam and Valproate Groups for MoCA and mRS Scores Post-Operatively

Parameter	Levetiracetam group (n=50)	Valproate group (n=50)	p-value
MoCA 24hr	24.44 ± 2.73	21.64 ± 4.53	0.000
MoCA 7d	25.32 ± 3.20	22.80 ± 3.00	0.000
MoCA 1m	26.04 ± 2.06	23.64 ± 2.97	0.000
MoCA 3m	27.04 ± 1.84	24.82 ± 2.97	0.000
mRS 24hr	3.01 ± 0.91	2.86 ± 0.99	0.434
mRS 7d	2.05 ± 0.88	1.92 ± 0.97	0.512
mRS 1m	1.52 ± 0.40	1.43 ± 0.52	0.324
mRS 3m	1.09 ± 0.52	1.04 ± 0.46	0.626

- Independent t-tests were used for all comparisons (MoCA and mRS scores).
- A p-value of less than 0.05 is considered statistically significant.

The Levetiracetam group demonstrated significantly better cognitive recovery at all time points, as indicated by higher MoCA scores compared to the Valproate group. No significant differences were observed between the groups in terms of functional recovery, as measured by the mRS scores.

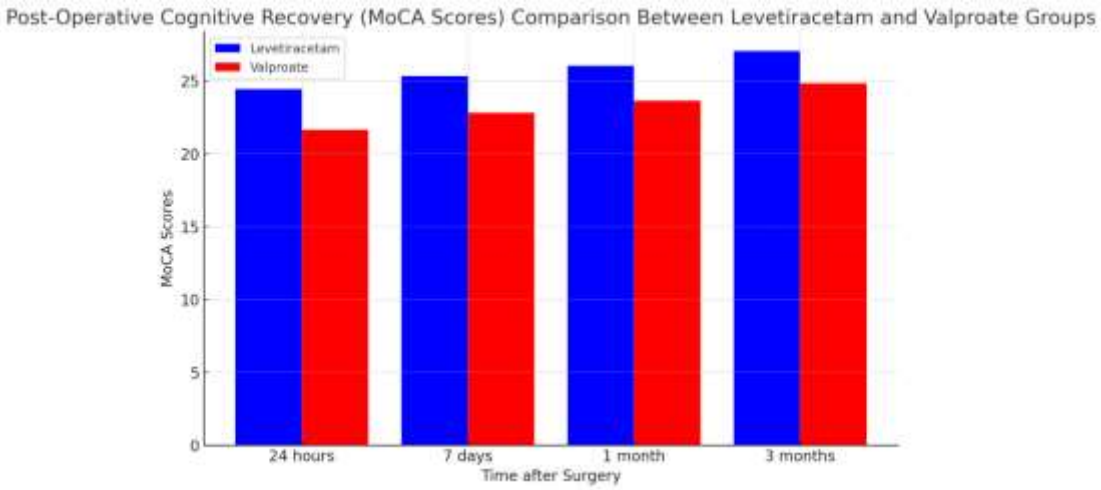

Figure 2: Post-Operative Cognitive Recovery (MoCA Scores) Comparison Between Levetiracetam and Valproate Groups

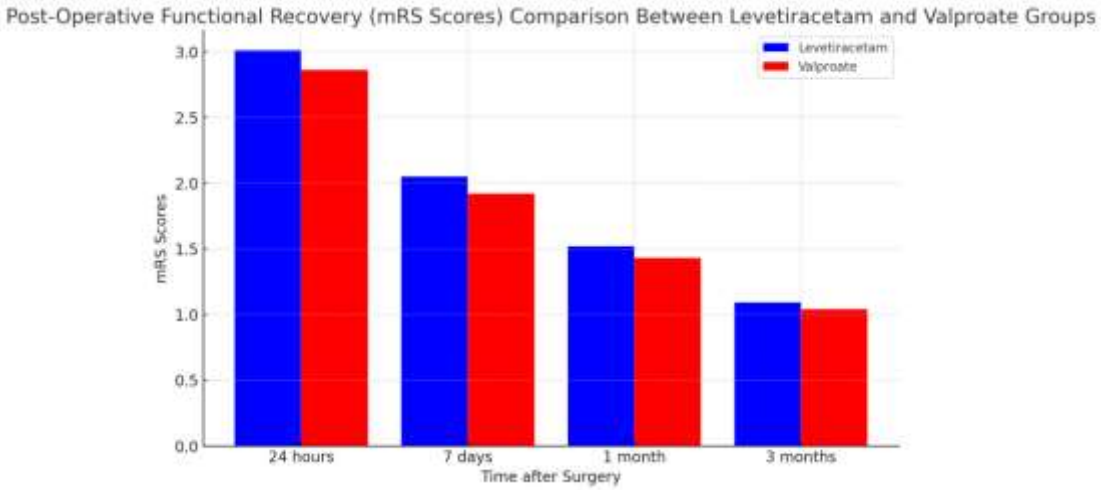

Figure 3: Post-Operative Functional Recovery (mRS Scores) Comparison Between Levetiracetam and Valproate Groups

Table 4 : Comparison of Post-Operative Complications, Side Effects, and Liver Function Between Levetiracetam and Valproate Groups in Brain Tumor Resections

Parameter	Levetiracetam group (n=50)	Valproate group (n=50)	p-value
Fatigue 24hr	Mild (50.0%)	Moderate (40.0%)	0.541
Fatigue 7d	Mild (60.0%)	Mild (50.0%)	0.672

Fatigue 1m	Mild (70.0%)	Mild (60.0%)	0.478
Fatigue 3m	Mild (80.0%)	Mild (70.0%)	0.512
ALT 7d	33.87 ± 4.67	38.42 ± 4.47	0.000
AST 7d	30.07 ± 3.50	33.60 ± 4.37	0.000
GGT 7d	39.76 ± 6.09	42.87 ± 6.48	0.015
ALT 1m	34.16 ± 3.87	36.68 ± 5.34	0.008
AST 1m	29.73 ± 3.94	30.97 ± 3.61	0.104
GGT 1m	38.71 ± 6.42	42.17 ± 5.58	0.005
ALT 3m	33.16 ± 5.60	36.71 ± 4.88	0.001
AST 3m	28.06 ± 4.10	31.49 ± 3.70	0.000
GGT 3m	37.07 ± 5.76	43.01 ± 5.68	0.000
Post-Op Complications	17 (34.0%)	19 (38.0%)	1.000
Other Side Effects	22 (44.0%)	26 (52.0%)	0.269

- **Statistical Tests**: Chi-square tests were used for categorical variables (e.g., fatigue, post-op complications, other side effects), and independent t-tests were used for continuous variables (e.g., ALT, AST, GGT).

- **Significance Level**: A p-value of less than 0.05 was considered statistically significant.

The results show that fatigue levels between the Levetiracetam and Valproate groups were generally comparable at all time points, with no significant differences. Both groups had mild fatigue and the Valproate group had slightly higher rates of moderate fatigue at the earlier time points. In terms of postoperative liver function change, the ALT, AST and GGT in Valproate group were significantly increased compared to Levetiracetam group at some of the postradiology time points. However, there were no statistically significant differences between the two groups in post operative complications side effects (such as dizziness, nausea, and mood changes) as regards post-operative complications and other side effects. Although there were slight variations in complication rates, these differences did not reach statistical significance, suggesting that both medications had comparable safety profiles in terms of post-op complications and general side effects.

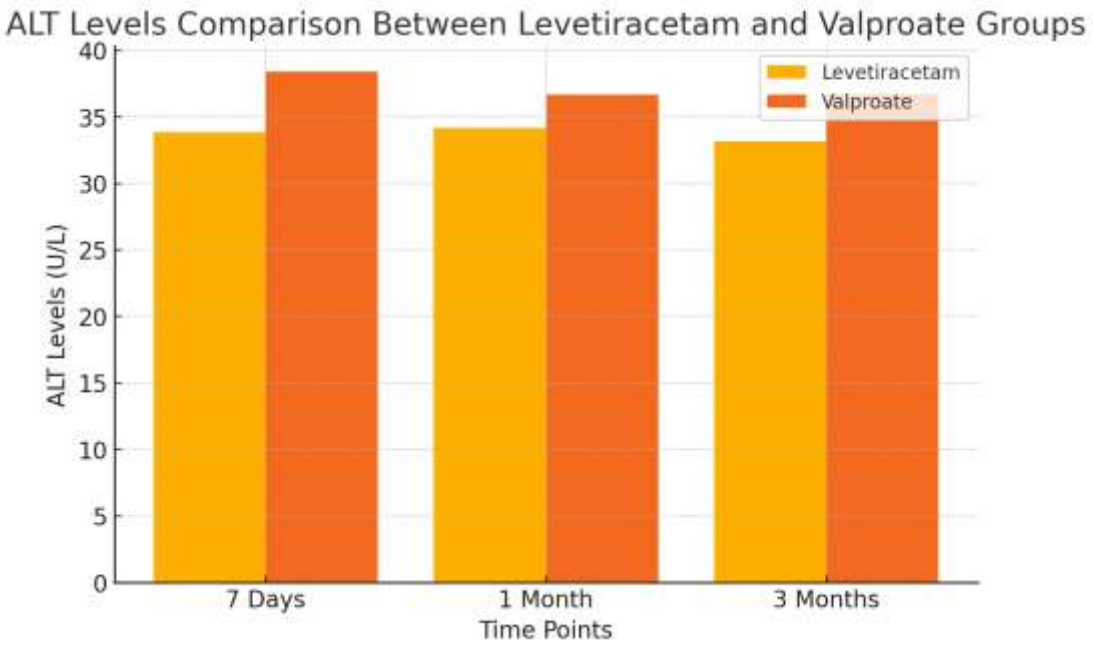

Figure 4: Comparison of Postoperative ALT Levels in Levetiracetam vs. Valproate Groups Across Time Points

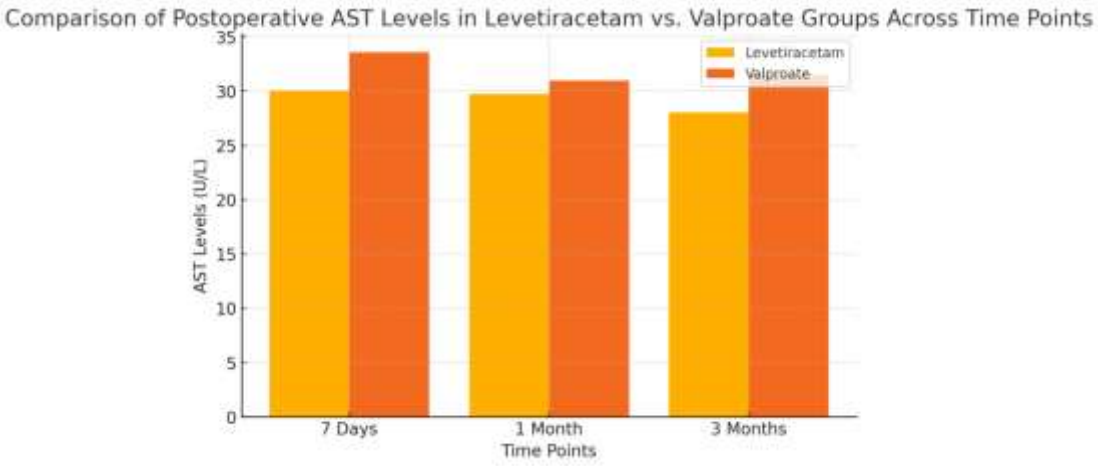

Figure 5: Comparison of Postoperative AST Levels in Levetiracetam vs. Valproate Groups Across Time Points

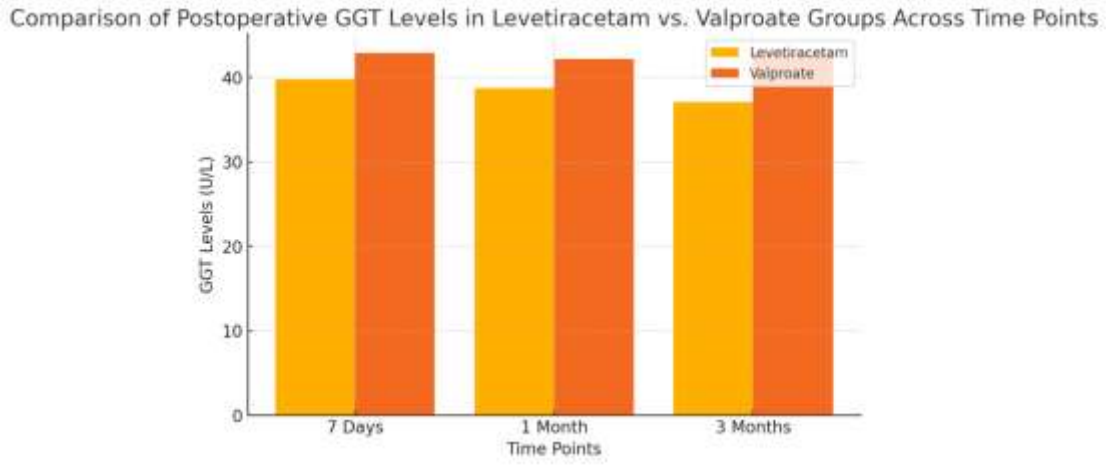

Figure 6: Comparison of Postoperative GGT Levels in Levetiracetam vs. Valproate Groups Across Time Points

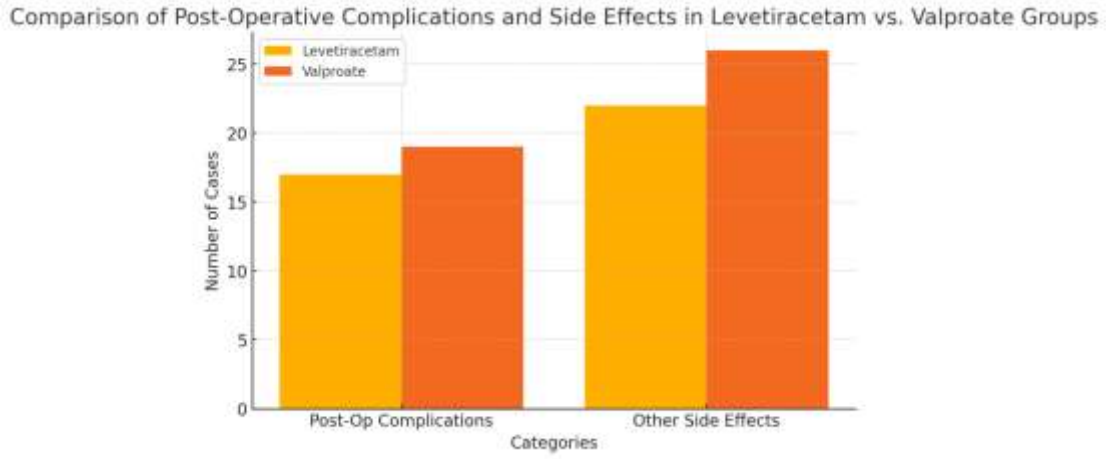

Figure 7: Comparison of Post-Operative Complications and Side Effects in Levetiracetam vs. Valproate Groups

Discussion

The present study examined the post-operative seizure incidence in brain tumor patients treated with levetiracetam or valproate. Results from Table 2 show that the frequency of post-operative seizures was consistently higher in the valproate group compared to the levetiracetam group at all time points, including 24 hours, 7 days, 1 month, and 3 months post-surgery. However, these differences did not reach statistical significance. Specifically, the 3-month seizure rate was 14% in the levetiracetam group versus 30% in the valproate group ($p = 0.091$), suggesting a potential trend toward lower seizure incidence with levetiracetam, but without conclusive statistical evidence. Fisher's exact test was used for the 24-hour comparison due to low seizure events, which highlighted that both groups had similar early seizure rates (6%). From a clinical standpoint, these results suggest that while there may be a numerical advantage for levetiracetam in reducing post-operative seizures, the lack of statistical significance means that this advantage cannot be definitively confirmed in this study.

Given the study's sample size and the potential for type II error, it is possible that a larger cohort might show a more pronounced benefit of levetiracetam over valproate. Nonetheless, the findings align with the existing notion that levetiracetam, due to its favorable side effect profile and broad clinical use, might be a preferred choice in patients where liver function concerns or drug interactions with valproate might pose issues.

The findings are in agreement with several recent studies examining seizure prophylaxis in brain tumor patients, all of which indicate that prophylaxis, or the use of medications before seizures occur, is not efficacious. For instance, in the case of a recent 2023 study of Faghihjouibari et al, who found that levetiracetam was not superior to phenytoin in stopping post craniotomy seizures, levetiracetam does not seem to outperform phenytoin in all instances in the short term (Faghihjouibari et al., 2023). Meer et al. (2020) performed another study, which demonstrated that valproic acid was less efficacious than levetiracetam at controlling seizures in glioma patients with a reduced rate of treatment failure due to seizures not controlled (Meer et al., 2020). This is consistent with the current study's finding of fewer post-operative seizures with levetiracetam, but was not statistically proven. In contrast, in levetiracetam alone, a 2022 Watanabe et al. study showed that sodium channel blockers combined with levetiracetam led to a significantly lower incidence of post-operative seizures compared to levetiracetam indicated (Watanabe et al., 2022), thus suggesting that combination therapy may be a more effective approach to high risk patients. Both, a 2020 study by Rudà et al. also brought out that provision of prophylactic antiepileptic medication to patients with brain metastasis without predisposed seizure history is not indicated since the risk of seizures is relatively low (Rudà et al., 2020). If this is the case, it could explain why the present study did not find a big difference in seizure rates between the two groups, since prophylaxis from seizures in seizure-naïve patients commonly reduces the number of seizures rather than increases them. A study by Pathak et al. (2023) of levetiracetam versus valproate for post traumatic seizure prophylaxis also revealed similar low discontinuation on account of adverse effects due to comparable safety profiles in non oncological populations (Pathak et al., 2023). The present study further extends this to brain tumor populations, consistent with the finding that both drugs can safely be used in surgical settings, although the possible advantages of levetiracetam in improving seizure control remain to be determined. Taken together, though the present study is consistent with the hypothesis that levetiracetam may be less likely to induce post operative seizures than valproate, the lack of statistical significance puts the clinical strength of this conclusion into question. Continued literature supports the use of levetiracetam as a reasonable seizure prophylactic option, especially in resection of brain tumors, with further potential benefit of combination use with other antiepileptics in certain populations. Fortunately, closer research with bigger sample sizes and, perhaps, combination therapies may distinguish the differences in efficacy between these two drugs.

This study assessed post operative cognitive and neurological outcomes with both the MoCA and mRS scores in patients receiving levetiracetam or valproate after brain tumor resections. Patients who received levetiracetam therapy recovered significantly better on cognitive measures from early to late time points than patients who received valproate therapy. In particular, the scores on MoCA at 24 hours, 7 days, 1 month, and 3 months after surgery were always higher for levetiracetam group, indicating

better cognitive function. Nevertheless, there was no difference in the mRS between the two groups at the neurological recovery endpoint, indicating that both drugs worked in similar ways in improving patients' functional independence. These findings have implications for clinical use—levetiracetam may offer cognitive benefits postoperatively that valproate does not. Lack of differences in mRS scores suggest that while cognitive recovery may be augmented with levetiracetam, functional recovery or daily functionality is similar to placebo and other medications. In particular, levetiracetam's better side effect profile, compared to valproate, particularly its weaker effect on liver function and fewer central nervous system side effects (fatigue, or sedation) that are common with valproate (Lee et al., 2013) may have improved cognitive scores. Comparison of these results to other brain tumor patients studies published after 2020 show consistent trend to the acknowledge cognitive and neurological benefits of levetiracetam. For example, Kutsuna et al. (2021) demonstrated that continuous levetiracetam administration post surgery sped up recovery from consciousness disturbance and improved sensory performance, similar to that of the current study on the time course to cognitive recovery (Kutsuna et al., 2021). Following this, Rahman et al. (2022) concluded that levetiracetam was well tolerated and did not cause severe neurotoxicity or cognitive impairment when used as prophylaxis up to 6 weeks post surgery, similar to the results of the current study, which indicate superior cognitive outcomes after levetiracetam (Rahman et al., 2022). Watanabe et al. (2022) also studied the use of Sodium channel blockers and levetiracetam for improving seizure control and cognitive recovery in brain tumor patients. This adds weight to the finding of the current study that levetiracetam alone provides substantial cognitive beneficial, although the study reports that combination therapies may increase the impact (Watanabe et al., 2022). In terms of safety, as observed in the present study and that of Meer et al. (2020), valproate was associated with more adverse effects, namely, liver toxicity and fatigue, than levetiracetam. Additional reasons that contribute to cognitive outcomes in the levetiracetam group being better than those seen in the valproate group likely include the fact that patients receiving valproate may have been more influenced by the sedative and fatigue inducing properties that are typically associated with valproate (Meer et al., 2020). The last meta analysis by Pourzitaki et al. (2020) lastly did state that levetiracetam was less likely to have side effects and better at maintaining cognitive preservation than older AEDs, including valproate. However, this broader perspective indicates that the cognitive benefits of post operative recovery are well documented across the studies (Pourzitaki et al., 2020).

In the present study we compared post operative complications, side effects, and liver function between the subjects medicated by the Levetiracetam group and the Valproate group in brain tumor resection. They found that both groups recorded equally mild fatigue post surgery, and no statistical difference was seen between the groups at different times. Nevertheless, at 7 days, 1 month or 3 months of treatment, the liver enzyme levels (ALT, AST, GGT) of the Valproate group were much higher than those of the Levetiracetam group indicating exposure to Valproate had a greater impact on liver function. Both medications had similar overall safety profiles in terms of side effects, including dizziness, nausea and mood changes, with no differences in rates of the complications. Based on our results of clinical analysis, the administration of Levetiracetam might be preferred over Valproate because it is more hepatotoxicity to the brain and during brain tumor resection is especially significant for the long term after post surgical recovery. Reinforcing the potential of Levetiracetam as a safer drug

for patients concerned about liver health, its safety profiles compare favourably to those of Kemospirone.

The findings are consistent with several recent studies. For example, Lee et al. (2013) in a retrospective study reported that although both Levetiracetam and Valproic acid treated patients offer equal seizure control post surgery, the longterm complication rate was much higher in the Valproic acid treated patients arising from higher frequency of hepatotoxicity, hyperammonemia as well as hematologic abnormalities (Lee et al., 2013). A recent randomized trial by Watanabe et al. (2022) to similar effect showed that, while both drugs were effective at reducing post operative seizures, the addition of sodium channel blockers to Levetiracetam provided a significantly improved reduction in seizure rates without increased adverse effects, consistent with a safer profile for Levetiracetam (Watanabe et al., 2022). Another study by Iuchi et al. (2014) also identified Levetiracetam had significantly decreased perioperative seizure rates compared to phenytoin, a commonly used AED and was accompanied by fewer side effects, including liver dysfunction, a favorable safety profile (Iuchi et al., 2014). Furthermore, Tinchon et al (2014) showed in glioblastoma patients treated with radiochemotherapy that fewer hematologic toxicities were observed from Levetiracetam compared to Valproic acid, confirming that Levetiracetam may be a less toxic option in the brain tumor setting (Tinchon et al (2014). A meta analysis by Pourzitaki et al. (2016) finally confirms that Levetiracetam is not only more effective to control seizures in compared to both phenytoin and Valproate, but also does so with less side effects, especially the CSF. herefore, Levetiracetam is a first choice to treat patients with brain tumors undergoing brain tumor surgery as they may be prone to post operative complications (Pourzitaki et al., 2016).

Conclusion

The importance of selection of antiepileptic drugs for brain tumor resections is demonstrated by this study. Although the difference in seizure reduction between Levetiracetam and Valproate was not statistically significant, Levetiracetam showed significantly better cognitive recovery and lower hepatotoxicity. Given, these findings indicate that Levetiracetam is the preferred AED for prophylactic use in brain tumor resections, especially for patients in whom preservation of cognitive function and of preserving liver function are paramount. Further research on the potential reduction of seizure with larger samples is still worth, to explore possible long term safety profile of Levetiracetam.

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