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The need for valproic acid as prophylaxis in neurosurgery patients

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Abstract: Using anti-epileptic drugs in neurosurgery patients is a routine practice. This controlled trial aimed to assess whether prophylaxis with *Valproate* in brain surgery patients is justified or not. Group A (n=50; controls) patients received valproic acid postoperatively for three months, while group B (n=50; subjects) received a placebo. Serum valproic acid levels between 50-125g/ml were required. Kendall's Tau was applied to see the correlation between the 'frequency of seizures' between different surgical procedures performed and the extent of manipulations-EOMs. A wireless EMOTIV EPOC device was used to visualize the Electroencephalogram patterns. In controls, 12 patients had one seizure and only two patients had 2 seizures. In the placebo group, 13 patients had one and 4 patients had 2 seizures. The seizure frequency was highest amongst brain tumor patients. An insignificant difference was found between the seizure frequencies of the placebo and control groups. A statistically insignificant correlation was found between seizure frequency and independent variables: surgical procedures and EOM (%). Using an AED or not, the frequency of seizures did not substantially reduce over the postoperative period. If not necessary, the anti-epileptic medication that is frequently provided as a prophylactic against seizures in the post-operative period should not be administered.

Keywords: Anti-epileptic drugs (AEDs), seizures, brain tumors, prophylaxis, trauma, hydrocephalus.

INTRODUCTION

Anti-epileptic drugs (AEDs) are frequently prescribed as a prophylaxis measure in patients with brain lesions. These drugs used to continue for 1-2 years after certain surgical interventions (biopsy, craniotomy, etc.) even though the patients were not having actual seizures (Wen *et al*., 2006). This study focused on the need for prophylactic use of valproic acid in patients after surgery for three months unless required. 'Unless required" refers to the notion that AED usage should not be withheld in patients who started having seizures following surgery. Such patients need seizure medication. Epilepsy is effectively controllable alone with medicines except for 20-30% of the refractory cases. Such cases may require surgical treatment for better control of seizures. Seizures can be caused by any intracranial lesion. Brain tumors, infective foci/abscesses, cysts, or hemorrhages can be the foci of irritation and causative of a lowered seizure threshold in the neurons and hence cause epilepsy. About 10-40% of brain tumor patients present with epilepsy. Seizure incidence is higher in primary tumor lesions as compared to metastases. Also, it is higher in low-grade compared to high-grade tumors (Lehnertz *et al.,* 2003). Generally, an anti-epileptic drug (AED) is initially used, however, poly-therapy may be needed in some patients for effective control. Surgical treatment requires a detailed seizure evaluation, including its character, frequency, type, psychosocial functioning, site of onset and grade of disability. Valproic acid, valproate and Semi-sodium *Valproate* are various forms of the same formulation used to treat epilepsy. Valproic acid is used at a dosage of 1000-2000 mg per day in two divided doses, never exceeding a maximum dose of 2500 mg per day (Chang *et al.,* 2003). The benefits of *Phenytoin*, valproic acid and *Carbamazepine* as prophylactic medicines for seizure control had not been proven in a randomized controlled trial (Sirven *et al.,* 2004) in brain tumor patients that underwent excision. A seizure incidence could be of high as up to 35% in brain tumor patients. Fast-growing malignant tumors like Glioblastoma cause symptomatic seizures (Rosati *et al.,* 2010). Slow-growing and benign tumors often exhibit epilepsy. The location of the tumor has a vital role in epileptogenesis. Superficial or cortical tumors often exhibit seizures compared to deeper structures (Shimony *et al.,* 2016).

Post-traumatic brain injury affects all age groups, but mostly younger patients (Varelas *et al.,* 2017). Annegers *et al.,* (1980) studied the incidence of seizure occurrence in more than 2000 brain trauma patients and concluded that 7-11.5% incidence of seizure occurrence was found in head injuries. Vespa *et al.,* (1999) reported that *Phenytoin* therapy in the first year after an injury did not prevent late seizures. Temkin *et al.,* (1999) found the competence of *Phenytoin* at reducing seizures spanning only one-week post-injury. Foy *et al.,* (1992) observed no significant differences between the subjects and controls regarding the incidence of seizures. Khan and Benerjee

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(2011) concluded that there may be a place for prophylactic anticonvulsants in brain trauma and seizures and further randomized controlled trials are needed to establish it. It has been reported that a brain abscess is invariably responsible for seizures in most patients. It was mentioned that brain abscess patients presenting with seizures should be considered for long-term antiepileptic medication (Kilpatrick, 1997). Maschio (2012) also studied the incidence of epilepsy in brain tumors which was 35 -70%. Surgeries that impact the anterior and posterior cranial fossae put more at risk of seizures. Epilepsy incidence primarily depends on the pathology of brain hematoma, abscesses and head trauma of the brain causing a higher incidence of postoperative seizures. The location of tumors in the brain also determines the postoperative seizure frequency. Most frequent meningiomas to cause epilepsy are located in the falx or parasagittal locations (Beenen *et al.,* 1999). Epilepsy in developing countries is highly attributable to bacterial infections of the brain. Seizures represent a long-term complication of bacterial meningitis. *Streptococcus pneumoniae* causes the highest incidence of seizures. Seizures that occur late involve risk factors like the occurrence of early seizures in the acute stages of meningitis and persistent deficits in the neurological system (Murthy & Prabhakar, 2008).

Commonly, *Valproate* has many side effects, i.e., gastrointestinal upsets, nausea, vomiting, poor appetite, liver dysfunction, cognitive impairment, hair fall, weight gain, myelosuppression and skin reactions (minor rashes to life-threatening Steven-Johnson syndrome) (Zerjav & Stowe, 2007). It was also noted that *Phenytoin, Valproate* and *Carbamazepine* when given in the presence of corticosteroids, greatly reduce the efficacy of the steroids. In addition, enzyme-inducing AEDs stimulate the activity of the cytochrome p 450 system and accelerate the catabolism of chemotherapy drugs. This can also result in chemo failure, increased relapse and recurrences of tumors. Conversely, corticosteroids and many other chemotherapeutic drugs interfere with the anticonvulsants in their metabolism, resulting in their over or under-dosage. The AEDs have also immunosuppressive effects and bring the immunity of patients down. This adds an insult to injury where immunity is already compromised (Glantz *et al.,* 2000). Bodilsen *et al.* (2023) investigated epilepsy risk variables and prognosis in brain abscess survivors. Seizures after brain abscess hospitalization, neurosurgery, drinking, frontal lobe abscess and stroke were all significant risk factors for epilepsy. Epilepsy was linked to an increased risk of death. Individual risk profiles may guide antiepileptic therapy and greater mortality in epilepsy survivors highlights the importance of specialist follow-up. Seizures in the immediate postoperative period might impede patient recovery and raise the risk of complications. A recent comprehensive analysis (2023) investigated whether postoperative seizure prevention after meningioma excision had any benefit. A total of 3,249 individuals were assessed over nine investigations, with 984 receiving AEDs. A study of patients who got AEDs against those who did not revealed no significant difference between the two groups. Postoperative seizures occurred in 5% of the patients (7 days) and 9% of the patients (>7 days), with substantial heterogeneity. The rate of postoperative seizures in seizure-naive patients was 2% in the early period and climbed to 6% in the late-term. The available data does not support the use of prophylactic AED drugs to prevent postoperative seizures in individuals having meningioma excision. This emphasizes the significance of using diagnostic criteria and doing individual patient analyses to aid clinical decision-making in this situation (Batista *et al*. 2023). Early post-traumatic seizures occur within 7 days after a traumatic brain injury and can result in further brain damage and poor results. *Levetiracetam* or *Phenytoin* are frequently used for seizure prevention, however, valproic acid may be a suitable treatment choice in patients with concurrent agitation. There is little evidence to support the use of valproic acid for both early post-traumatic seizure prevention and agitation. Nicole Gilliam *et al.,* (2023) investigated the safety and effectiveness of valproic acid for early post-traumatic seizure prevention as well as agitation. They discovered that valproic acid looks to be a promising treatment option for preventing early post-traumatic seizures in individuals with traumatic brain injuries and concurrent agitation, with few side effects. The current trial was conducted to know more detail about why extensively used AED when it's not needed. Therefore, randomized, controlled trials are required to better study valproic acid's involvement in this indication, including dosage regimen standards, serum drug monitoring and the link between valproic acid treatment and mortality.

MATERIALS AND METHODS

Study Design and Setting

This research was a randomized, double-blinded and placebo-controlled factorial trial conducted in the Department of Neurosurgery, Shaikh Zayed Hospital, Lahore. The duration of the trial was from March 2018 to March 2019 including follow-up. The included patients were the regional adults having an intracranial pathology.

Sample Size & Patient Groups

The sample size was calculated with a 5-6 % significance, 95% confidence interval and 80% power of test with an expected percentage of efficacies. The sample size was 100 patients (50 in each group; allocation ratio 1:1). The study included brain pathology requiring surgery. Fifty (n=50) patients were the controls who received an anti-epileptic drug (Group A), whereas, fifty patients (n=50) were grouped as a study group who received a placebo. CONSORT (2010) guidelines were followed for this

randomized controlled trial (RCT). Once the patient has agreed to participate in the trial, he or she is randomized. The patients were randomized into two groups under consecutive sampling from the lottery method. In this strategy, the researcher assigned a number to each member of the population. To choose samples, the principal investigator plucked the numbers at random from a box. With simple random allocation, we selected the patients for treatment and control groups purely at random, with no consideration for the researchers' intent or the patient's condition and preferences. It was ensured that the number of patients assigned to each group was dispersed equally. The process of randomizing patients in this trial had three steps: sequence generation, allocation concealment and implementation. The patients were effectively (though covertly) assigned to subject/control groups (to eliminate selection bias and minimize confounding variables). The patients and investigators were blinded to which group each patient was assigned. The result was examined by an investigator who was blind to the treatment allocation. Patients were studied within the group to which they were assigned, regardless of whether they received the specified treatment (intention to treat analysis).

Clinical Management

Valproic acid was given for three months in controls (Group A) in symptomatic patients who exhibited seizures. The study group (subjects) received a placebo for three months. The control group patients received the AEDs, right after the surgery and continued for a minimum of three months, regardless of the occurrence of seizures.

Inclusion & Exclusion Criteria

Patients included both genders ranging from 16-70 years of age. Patients included those who underwent brain surgery for any of these intracranial pathologies (tumor, trauma, hemorrhage, abscess and hydrocephalus). Patients taking any other antiepileptic drugs prescribed previously were excluded. Patients having any medical implants like cardiac pacemakers aneurysmal clips in the brain or cochlear implants were not included. Cases of a previous history of epilepsy, pregnant women, cigarette smokers and those who take heavy caffeine. Patients excluded who did not comply with visits/follow-ups.

If patients from the placebo group developed seizures during the study, they were excluded from the group and replaced with new patients, to maintain the sample size (n=50). Patients with a progressive disease that interferes with study objectives and Karnofsky Performance Scale (KPS) score below 30 were also not included.

Valproic acid levels

The valproic acid levels were checked to ascertain adequate therapeutic effects for one month. Adequacy of valproic acid in serum (50-125µg/ml) was maintained avoiding their toxic levels.

Data Collection

Patients were admitted through emergency and OPD (out-patient door) departments. Patients with confirmed brain lesions fulfilling inclusion and exclusion criteria were enrolled in the Department of Neurosurgery. Informed consent was taken from all patients or their attendants. The routine laboratory tests were conducted for the CBC, PT (partial thromboplastin time), APTT (activated partial thromboplastin time), renal and liver profiles, etc. A standard dose (500 mg twice daily) of valproic acid was administered to the control group (A). Cardiovascular fitness for general anesthesia was also assessed. Radiological investigations like CT and MRI (with or without the IGS-image-guided surgery protocol) were also performed. The clinical history of all enrolled patients who underwent the specific surgical procedure on brain lesions was taken including demographic data. Fifty patients were grouped as the 'study group' and received a placebo, whereas the other 50 patients (controls) were given Valproic acid for 3 months. We used a digital, wearable, rechargeable and wireless *Emotiv Epoc* (14 channels) electroencephalogram (EEG) to visualize the seizure pattern. *Emotiv EPOC* is a high-resolution, multi-channel, wireless neuroheadset. The EEGs were performed before surgery, after surgery (during hospital stay) and upon follow-ups.

Ethical approval

The study was conducted after approval (reference number: 1-27/M.Edn/53/2018) from the ethical review board of the Federal Postgraduate Medical Institute, Shaikh Zayed Hospital, Lahore, Pakistan.

STATISTICAL ANALYSIS

SPSS version 25 was used for the calculations. Mean age (mean±SD), sex, the surgical procedure performed, the extent of manipulation (EOM) seizure frequencies, etc. were calculated in each group. The data was checked for its normality with the Shapiro-Wilk test. The data was not normal and therefore, nonparametric tests Spearman's rho and Kendall tau were applied. Mann-Whitney (U) test was conducted for the comparison of seizure frequencies between groups. Two non-parametric correlation analyses (Kendall's Tau and Spearman's Rho) were performed to see the correlation between the 'frequency of seizures' (dependent variable) by following independent variables: (i) type of surgical procedure performed and (ii) extent of manipulation-EOM. The correlation coefficients were obtained and analyzed to observe the strength and direction of the correlation. A significant difference was observed at a p-value <0.050.

RESULTS

Clinical and Background Information

A total of 16 patients were excluded from the placebo (group B) as they developed seizures and required

management with oral or I/V AEDs as per seizure management protocols. Twenty-five new patients were added to compensate for those cross-over patients. Nine out of these 25 patients developed seizures and were excluded again. The remaining 16 patients continued in the placebo group. Information on the gender and age group of patients of both groups A and B are represented in tables 1 and 2. There were 11 (22%) cases of trauma, 8 (16%) cases of infection, 27 (54%) cases of brain tumor *and* 5 (10%) cases of hydrocephalus in the control (Group A), while, there were 12 (24%) cases of trauma, 9 (18%) cases of infection, 23 (46%) cases of brain tumor and 5 (10%) cases of hydrocephalus in the placebo (Group B) (table 3). Tables 4 to 7 show detailed explanations regarding each pathology included. Table 8 shows detailed information regarding Karnofsky performance scale scores in both of the groups, before surgery, on the third day of surgery *and* follow-up. Table 9 shows the distribution of surgical procedures performed in both groups and table 10 shows the distribution of Extent of Manipulation performed (EOM %) in both groups.

Valproic acid levels and seizure frequencies

Valproic acid evaluation in patients after brain surgery including ventriculoperitoneal shunts (VP) was carried out by monitoring serum *Valproat*e levels or through the electroencephalogram (EEG). The mean serum Valproate level was 87µg/ml in the control group. There were 36(72%) patients with no seizure frequency in three months, 12(24%) patients having one seizure in three months and there were 2(4%) patients were having two seizures in three months in the control (Group A), while, there were 33(66%) patients with no seizure frequency in three months, 13(26%) patients were having one seizure in three months and there were 4 (8%) patients were having two seizures in three months in the placebo (Group B) (table 11). In controls (Group A), only two patients had 2(4%) seizures, during the study. Whereas, in placebo (Group B), 4(8%) patients had 2 seizures, during the study. The seizure frequency was highest amongst brain tumor patients followed by trauma and infection in both groups (table 12).

Comparisons and correlations

According to the Mann-Whitney U test, an insignificant difference (p-value: 0.96>0.050; z-score: 0.168) was found between the seizure frequencies of placebo and control groups. The results of this test indicate that there was no clinical reduction in seizure frequency in groups who were taking AEDs (controls) and who were taking a placebo. A statistically insignificant correlation was found between the dependent variable (seizure frequency) and independent variables: surgical procedures (craniotomy, biopsy, VP shunt & evacuation) and EOMs% (total resection of the lesion, subtotal resection, partial resection of tumor/ hematoma evacuation, needle instrumentation including hematoma aspiration/ needle biopsy) at p values greater than 0.050 (table 13).

Complications

During 3 months in group A, the following complications were observed: dizziness (56%), sleep disturbance (38%), deranged LFTs (24%) and weight gain (12%).

Electroencephalogram (EEG) patterns

Fig. 1 shows an EEG from a patient in the control group, indicating seizure activity and temporal lobe epilepsy. Fig. 2 shows an EEG of a patient of a Placebo group, indicating seizure activity in parietal lobe epilepsy. Fig. 3 shows a post-prophylaxes EEG of a patient of the control group.

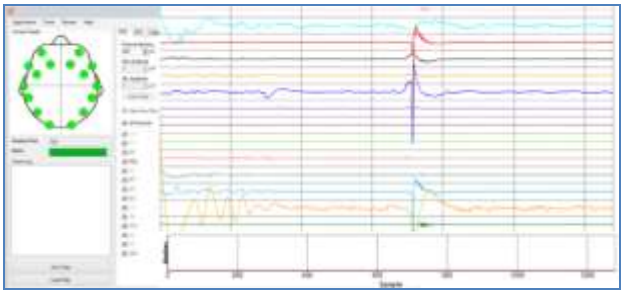

Fig. 1: EEG (Control group) Showing Seizure Activity. Temporal Lobe Epilepsy in Control Group Patient). Right temporal lobe showing ictal activity in due course of seizures. The EEG response remained localized to the same anatomical location.

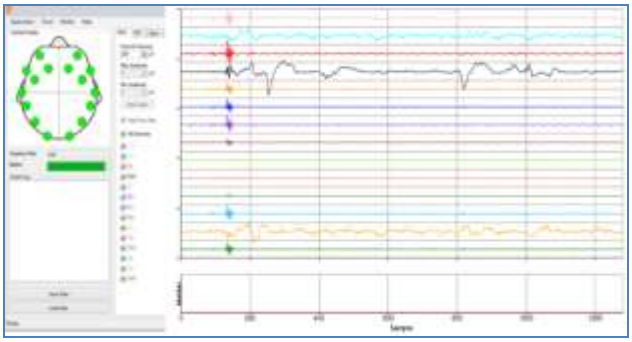

Fig. 2: EEG Showing Seizure Activity in Placebo Group**.** Maximum onset of seizure at left Parietal Lobe at electrode 4 position.

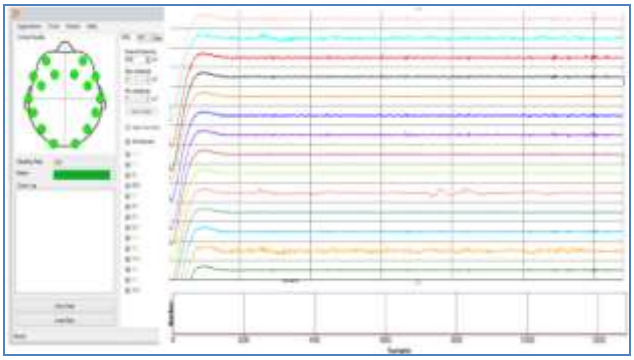

Fig. 3: Post prophylaxis EEG

Table 1: Gender distribution in Groups A (n=50) & B (n=50)

Gender	Groups		Total
	Control	Placebo	
Male	36(72%	34(68%)	70%
Female	14(28%)	16(32%	30%

Table 2: Distribution of age in Groups A (n=50) & B (n=50)

Age groups (years)	Groups		Total
	Control	Placebo	
16-30	18(36%)	11(22%)	29%
31-50	20(40%)	18(36%)	38%
51-80	12(24%)	21(42%)	33%

Table 3: Distribution of diagnosis in Groups A (n=50) & B (n=50)

Type of Diagnosis	Groups		Total
	Control	Placebo	
Trauma	11(22%)	12(24%)	23%
Infection	8(16%)	9(18%)	17%
Tumor	27(54%)	23(46%)	50%
Hydrocephalus	5(10%)	5(10%)	10%

Table 4: Distribution of trauma cases (n=23) in both groups

Diagnosis: Trauma	Groups		Total (n=23)
	Control (n=11)	Placebo (n=12)	
Unilateral Chronic SDH (Subdural hematoma)	1(9.1%)	1(8.3%)	2(8.69%)
Acute SDH (Subdural hematoma)	2(18.2%)	3(25%)	5(21.7%)
EDH (Extradural hematoma)	4(36.3%)	3(25%)	7(30.4%)
Posterior Fossa Bleed	2(18.2%)	1(83%)	3(13.04%)
Intracerebral Bleed	1(9.1%)	1(8.3%)	2(8.69%)
Bilateral Chronic SDH	1(9.1%)	1(8.3%)	2(8.69%)
Others	0(0%)	2(16.6%)	2(8.69%)

Table 5: Distribution of infection cases (n=17) in both groups

Diagnosis: Infection	Groups		Total (n=17)
	Control (n=8)	Placebo (n=9)	
Left temporal lobe fungal infection	1(12.5%)	1(11.1%)	2(11.7%)
Fungal abscess	2(25%)	2(22.2%)	4(23.5%)
Right parietal lobe fungal infection	2(25%)	2(22.2%)	4(23.5%)
CSOM (chronic suppurative otitis media) cerebellar abscess	3(37.5%)	4(44.4%)	7(41.2%)

Table 6: Distribution of tumor cases in both groups, (n=50)

Diagnosis: Tumor	WHO Tumor Grade	Groups		Total (n=50)
		Control (n=27)	Placebo (n=23)	
Posterior fossa pilocytic astrocytoma	Grade I	1(3.7%)	1(4.34%)	2(4%)
Glioblastoma	Grade IV	6(22.2%)	5(21.7%)	11(22%)
Craniopharyngioma (Adamantinoma)	Grade I	2(7.4%)	3(13.04%)	5(10%)
Posterior fossa tumor (Astrocytoma)	Grade I/II	2(7.4%)	4(17.39%)	6(12%)
Pilocytic astrocytoma	Grade I	1(3.7%)	0(0%)	1(2%)
Meningioma	Grade I	2(7.4%)	3(13.04%)	5(10%)
Schwannoma	Grade I	3(11.11%)	2(8.69%)	5(10%)
Malignant Meningioma	Grade III	0(0%)	2(8.69%)	2(4%)
Glioma	Grade I/III	1(3.75%)	1(4.34%)	2(4%)
Astrocytoma	Grade II	2(7.4%)	2(8.69%)	4(8%)
Oligodendroglioma	Grade II	2(7.4%)	0(0%)	2(4%)
Craniopharyngioma	Grade I	1(3.7%)	0(0%)	1(2%)
Cerebral metastases		1(3.7%)	0(0%)	1(2%)
Intraventricular tumor (Ependymoma)	Grade III	2(7.4%)	0(0%)	2(4%)
Left occipito-parietal (Meningioma)	Grade I	1(3.7%)	0(0%)	1(2%)

Table 7: Distribution of cases of hydrocephalus (n=10) in both groups

Diagnosis: Hydrocephalus		Groups		Total
		Control (n=5)	Placebo (n=5)	
Etiology	*Due to tumor*	2(40%)	2(40%)	4(40%)
	Due to infections	1(20%)	2(40%)	3(30%)
	Due to trauma	2(40%)	1(20%)	3(30%)

Table 8: Distribution of Karnofsky Performance Scale (KPS) Scores

No. of Patients (Group A)	Control (Group A) Mean KPS Score			No. of Patients (Group B)	Placebo (Group B) Mean KPS Score			Total No. of Patients (Group A+B)
	Pre-Op	*3rd Post-Op Day*	*Follow up*		*Pre-Op*	*3rd Post-Op Day*	*Follow up*	
3	100	80	90	4	100	90	90	7
8	90	80	90	8	90	80	90	16
6	80	70	80	6	80	70	70	12
8	70	60	80	8	70	60	60	16
11	60	50	70	10	60	50	50	21
8	50	40	50	8	50	40	40	16
3	40	20	20	3	40	30	20	6
3	30	20	20	3	30	20	10	6

Table 9: Distribution of surgical procedure performed in both groups

Surgery type	Groups		Total
	Control	Placebo	
Craniotomy	30(60%)	20(40%)	50%
Needle Biopsy	5(10%)	5(10%)	10%
VP (Ventriculoperitoneal) Shunt	5(10%)	10(20%)	15%
Clot Evacuation	10(20%)	15(30%)	25(25%)

Table 10: Distribution of Extent of Manipulation performed (EOM %) in both groups

EOM %	Groups		Total
	Control	Placebo	
Total resection of the lesion	22(44%)	15(30%)	37%
Subtotal resection of lesion	14(28%)	10(20%)	24%
PR (partial resection of the lesion)	1(2%)	2(4%)	3%
Needle instrumentation aspiration/ biopsy)	13(26%)	23(46%)	36%

Table 11: Comparison of seizure frequency distribution in both groups

Seizure frequency (in 3 months)	Groups		Total
	Control	Placebo	
0	36(72%)	33(66%)	68%
1	12(24%)	13(26%)	25%
2	2(4%)	4(8%)	7%

Table 12: Number of Patients in Groups A and B with Seizures in Each Lesion

Seizure frequency (Three months)	Number of Patients in Group A with Seizures in each Lesion				Total number of patients with seizures
	Trauma (n=11)	Infection (n=8)	Tumor (n=27)	Hydrocephalus (n=5)	
0	8	5	20	4	36
1	3	2	6	1	12
2	0	1	1	0	2
Number of Patients in Group B with Seizures in each Lesion					
	Trauma (n=12)	Infection (n=9)	Tumor (n=23)	Hydrocephalus (n=5)	Total number of patients with seizures
0	9	6	14	3	33
1	2	3	7	1	13
2	1	0	2	1	4

Table 13: Correlation analysis between seizure frequency with surgical procedures and EOM (%)

	Analysis	Surgical Procedure	EOM (%)
Frequency of Seizures	*Kendall's Tau Correlation*	0.12	-0.072
	p-value	0.464	0.453
	Spearman's Rho Correlation	0.13	-0.081
	p-value	0.35	0.568

DISCUSSION

Valproic acid is not only ineffective in seizure prophylaxis in patients with cerebral lesions but may also pose more risk of complications in such patients. No sufficient evidence supports the use of *Valproic Acid*, *Phenytoin* and *Phenobarbital* as effective prophylaxis for surgical patients with brain tumors or infections. Studies regarding the prophylactic use of AEDs in brain tumors in seizure control have weak and mixed conclusions. Ever since a patient develops a cerebral lesion, he or she is generally given prophylactic medication for seizure control. Sometimes it is justified in case the patient exhibits seizures during his/her clinical stay in the hospital or at home. Such antiepileptic prophylaxis is not always needed. The seizure frequency was highest amongst brain tumor patients followed by trauma and infection in both groups. The two groups (controls who took AEDs and Placebo) were found statistically similar and the seizure frequency observed in them was independent of the use of the anti-epileptic drugs. The seizure frequency was also found to be independent of the extent of Manipulation (EOM) in different lesions. In our patients, the frequency of seizures did not improve significantly with or without AED in the postoperative period. In some of the patients that were recruited, distinct adverse effects of Valproic acid were also documented. In the control group, 72% of patients were found with no seizure frequency, 24% of patients had one seizure and there were only 4% of patients had two seizures. In the Placebo group, 66% of patients were found with no seizure frequency, 26% of patients had one seizure and 8% of patients had two seizures. Certain drugs tend to have raised serum levels due to interaction with valproic acid. We concluded that anti-epileptic drugs should not be used as a prophylactic against seizures in the post-operative period unless necessary.

Temkin (2002) reported that the frequency of seizures was reduced by 40-50% in the first week of use of AEDs (*Phenytoin, Carbamazepine and Phenobarbital*) between placebo and control groups of brain surgery patients. But, after one week, the effectiveness of any AED was markedly reduced. No benefits were seen in using prophylaxis seven days after trauma as reported by Chang and Lowenstein, (2003). Some other studies do not support the use of AEDs for prophylaxis against epilepsy in asymptomatic brain tumor patients (van Breemen *et al.*, 2007). Anti-epileptic did not prove effective in preventing seizures one week after the surgical intervention and also during the six months of follow-up. Also, patients with tumors and seizures did not benefit from anti-epileptics. However, it is the physician's judgment to weigh the risks of seizures versus the risks of AEDs. Failure of AEDs to prevent seizures in patients with brain tumors may be due to different reasons: (i) Many AEDs block potassium, calcium, or sodium channels or by augmentation of γ-aminobutyric acid. Tumors cause seizures either by altering peritumoral amino acids, changing local tissue pH and cellular metabolism, protein expression, glial enzymes and localized immunological changes, (ii) Size of tumors and their growth rate remain unaffected by AEDs and (iii) Poor maintenance of the serum concentrations of the AEDs and deficiencies in plasma proteins that transport the AEDs (26). *Valproate* therapy showed no benefit over short-term *Phenytoin* therapy for the prevention of early seizures. Both drugs failed to be effective in late seizures. Researchers have also found a higher trend toward high mortalities in patients taking *Valproate*. Moreover, no significant difference was also found in the intracranial pressures of both groups (Inglet *et al.,* 2016). A study included 128 brain tumor patients, 65 had pre-operative seizures and 63 without seizures. Of these 63 patients without seizures, 41 patients were given AEDs and the other 22 patients were not given any prophylactic drug. The study mentioned that some early postoperative patients should all receive AEDs; this prophylaxis should not exceed ten days, those who have a positive history of epilepsy should continue to take AEDs as long as the seizure guidelines suggest and any long-term use of AEDs in the seizure-free patients should be discouraged and discontinued from clinical practice. Sirven *et al.,* in 2004 reported a strong relationship between increasing the severity of brain trauma and the development of seizures. The raised incidence of seizures in the group with mild traumatic brain injuries may well be attributed to the individual characteristics and the health of the patients rather than the injuries. In a study of the late occurrence of seizures after traumatic brain injury, subdural hematomas and contused brain tissue proved to be the most significant risk factors. The studies advocate the use of epilepsy prophylaxis for not more than a week owing to prohibitive factors like poor efficacy and occurrence of side effects.

The incidence of seizures in patients with posterior fossa tumor surgery was recorded highest in acoustic Schwannoma followed by Medulloblastoma as mentioned

by Suri *et al.,* (2009). Decompressive surgeries performed for posterior fossa lesions can cause changes in fluid drainage. The fluid drainage was variable and was a noticeable risk factor for epilepsy, however, what is more, remarkable is that epilepsy was observed when decompression was performed for non-expanding lesions (hemorrhage) and less marked for space-occupying lesions like tumors as mentioned by Yacubian *et al.,* (1999). A high risk of seizures exists in aneurysmal subarachnoid hemorrhage. Other seizure-causing pathologies are meningioma, arteriovenous malformation and glioma. The higher the malignancy, the lower the incidence of seizures. Surgical infection, ischemia and surgical approach also exhibit their role in seizure incidence (Beenen *et al.,* 1999). In a randomized controlled trial on the use of valproate and phenytoin in post-craniotomy patients, the groups had no difference in the severity of seizures. Similar tolerability and efficacy were found in the same number of patients who had seizures. Various factors have been found responsible for seizures, especially *Streptococcus pneumoniae* infections. Factors like low GCS, diabetes, splenectomy, alcoholism, immune-compromised health status and HIV infection were also involved. A poor outcome was seen in epileptic patients than in those who did not develop seizures (Ellison *et al*., 2008). Central nervous system infections have been related to the causation of seizures. Bacterial infections of several types and severity have been observed in seizure cases. It has been found that the production of antibodies in the human body after bacterial infections was more noticeable in patients developing seizures. These patients did not have clinical signs or symptoms of infections, yet they developed seizures (Murthy & Prabhakar, 2008). Prophylaxis with AEDs is not indicated for individuals with brain metastases who have never had seizures. Seizures might be an unintended consequence of stereotactic radiosurgery or high-dose chemotherapy (Rudà & Pellerino, 2014). Sodium *valproate* can quickly cause hematologic toxicity (Lehnertz *et al.,* 2003). *Levetiracetam* and Valproic acid did not have statistically significant differences in postoperative seizure control rates; nevertheless, *Levetiracetam* may be better than Valproic acid in terms of safety and durability after supratentorial tumor surgery (Lee *et al.,* 2013). Two meta-analyses concluded that preventive therapy does not enhance seizure control in these individual (Sayegh *et al.,* 2014). On Valproic acid prophylaxis, there was a 40% chance of having a seizure. There were no severe side effects from the therapy (Valiyaveetti *et al.,* 2018). Yang *et al.,* (2020) hypothesized that preventive Valproic acid therapy did not help to alleviate perioperative seizures (Mori *et al.,* 2017). Patients who took seizure prophylaxis were often older, stayed in the hospital longer *and* died more frequently than those who did not. Sicker patients may be given seizure prevention first (Inglet *et al.,* 2016). The findings show that *Levetiracetam* may have better effectiveness than valproic acid, with equal levels of toxicity (van der Meer *et al.,* 2021).

Topiramate is useful in decreasing seizure frequency by at least 50% when used as an add-on medication for people with treatment-resistant focal epilepsy. Topiramate is three times as effective as a placebo. Even at the lowest dose of 200 mg per day, compared to the placebo group, roughly 20% more individuals reported a 50% reduction in seizure rate. According to the dosage regression model, as the dose is increased, the impact increases somewhat (Bresnahan *et al.,* 2019). *Lamotrigine* as first-line therapy for generalized primary or secondary seizures, as well as juvenile myoclonic epilepsy, because of its tolerance, fewer side effects and low prescription frequency (Ebrahimi & Ebrahimi, 2012). There was no difference between the treatment interventions and the control groups in terms of preventing the first seizure in those with brain tumors. The evidence is neither in favor of nor against seizure prevention in people with brain tumors (Tremont- Lukats *et al.,* 2008). *Carbamazepine* is less likely to be discontinued in patients with intermediate confidence evidence. Other outcomes, such as for those with generalized tonic-clonic seizures/unclassified epilepsy, revealed no differences between medicines; however, research involving small groups of people with specific seizure types should be read with caution (Nevitt *et al.,* 2017). Fonkem *et al.,* (2013) concluded that levetiracetam can make Glioblastoma tumors more sensitive to the chemotherapeutic medication *Temozolomide*. *Levetiracetam* is a safe alternative to traditional antiepileptic medicines and a promising treatment for seizures in brain tumor patients. More research on the advantages of utilizing AEDs as prophylaxis in patients with brain infarcts, diffuse brain tumors, or the requirement for awake craniotomies is needed, according to Kamenova *et al.,* (2020).

CONCLUSION: *Valp*roate should not be a routine practice as prophylaxis against early or late post-traumatic seizures because of minimal benefits and potentially higher mortality. Due to their poor efficacy and considerable side effects, their usual practice as prophylaxis should be discouraged.

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