Low Cholesterol as a Risk Factor for Spontaneous Intracerebral Hemorrhage

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ABSTRACT:

BACKGROUND:

More than 14 antiepileptic drugs (AEDs) have been licensed for use in epilepsy over the last 20 years. Levetiracetam (LEV) & topiramate (TPM) are two of the most commonly prescribed new AEDs. The comparison between different AEDs is a crucial issue for decision making in epileptology.

OBJECTIVE:

To compare the efficacy & safety of LEV vs. TPM as monotherapy or add-on therapy in focal onset or generalised epilepsy.

METHODS:

The study carried on 75 epileptic patients (45 on LEV vs 30 on TPM). Data were taken regarding age, gender, type, dosage & duration of treatment, type & frequency of seizures six months before & after therapy, & drug-related adverse reactions (ARs). For data analysis each therapy group is divided into mono or add-on therapy. Further subdivision into generalised or focal seizure was done. Efficacy was assessed as a percentage of reduction of monthly seizure frequency after LEV or TPM initiation compared to baseline.

RESULTS:

In the total samples; although LEV was better than TPM in overall seizure control, the difference was not significant (p-value = 0.1). Seizure freedom was 57.8% with LEV vs. 43.8% with TPM. Reduction ≥50% was achieved in 100% LEV vs. 90% TPM patients. Both showed high efficacy in generalised & focal seizures in both add on & monotherapy groups. In the subgroup analysis of monotherapy; LEV showed a higher rate of seizure freedom (83.3%) vs. 55.6% with TPM for treatment of generalised seizure. While for focal seizure, LEV showed 100% responder rate vs. 50% for TPM. Despite the above observations none of the two AEDs showed significant superiority over the other. Both were equally effective in paediatric & adult patients in high & low doses. Drug ARs were less frequent with LEV than TPM although both of them had reasonable safety profile.

CONCLUSION:

The efficacies of LEV & TPM were almost equal in treating focal or generalised seizures as mono or add-on therapy. Both were equally effective in adults & paediatric patients, in high & low doses. The safety profile of LEV was more favourable than TPM.

KEY WORDS : levetiracetam, topiramate, epilepsy, adverse reactions.

INTRODUCTION:

Epilepsy is a common chronic neurological disorder. In which the term 'epilepsy' embraces a constellation of seizures & syndromes, each manifest by recurrent seizures that result from abnormal, hypersynchronous or excessive neuronal activity. Approximately 50 million people suffer from this disorder worldwide with nearly 90% being in developing countries [1,2]. The primary target in the management of epilepsy is control & prevention of seizures. The achievement of seizure freedom is an essential outcome measure because it has the greatest impact on quality of life [3]. Excluding the small percentage of people who underwent successful epilepsy surgery, the vast majority of patients should have chronic medical management for appropriate seizure control. This often imposes an exposure to various anti-epileptic drugs (AEDs) & requires long-term commitment & compliance from the patient [4]. AED-resistant epilepsy is still evident in 20–30% of patients with seizure disorders [5]. Over the past 20 years, more than 14 AEDs have been licensed for use in the common epilepsies & a range of more unusual syndromes [6]. Commonly, a particular AED is chosen based on seizure types, a drug to drug interactions, metabolism, dosing

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convenience, comorbidities & side effect profile [4]. Among the most commonly prescribed ''new generation'' AEDs are TPM & LEV [3]. TPM is a broad-spectrum AED with multiple mechanisms of action, including the blockade of voltage-dependent sodium channels, potentiation of gamma-aminobutyric acid (GABA)-mediated effects, carbonic anhydrase inhibition & glutamate antagonism [7] & it has established efficacy as monotherapy & adjunctive therapy in both generalised & partial seizure in children & adult [8]. LEV is a newer AED with a unique mode of action that differs from that of currently available AEDs. The effect of LEV is mediated by the synaptic vesicle protein SV2A, resulting in an inhibition of neurotransmitter release from the end terminals. Also, it has a broad spectrum efficacy against focal & generalised seizures when it is used both as mono & add-on therapy [9,11]. The likelihood of adverse reactions (ARs) is an important aspect in the choice of AEDs prescribed to patients with epilepsy, since achieving the primary goal of epilepsy management; controlled seizures with minimum AEDs toxicity is a major challenge to the prescribers [12].

AIM OF THE STUDY:

To compare the efficacy & safety of LEV vs. TPM as monotherapy or add-on therapy in focal onset or generalised epilepsy with high or low dose in paediatric & adult patients.

METHODS:

Data collection

This work is a cross-sectional study. The data were collected from 75 patients with an established diagnosis of epilepsy attending the neurology outpatient clinic or admitted in the medical emergency or the general medical teaching hospital in Sulaimani city of the Iraqi Kurdistan Region from Feb. 2013 to Mar. 2014. History was taken from each case by using a particular questionnaire form that included: age, gender, family history, type & duration of treatment. Data about type & frequency of seizures six months before & 6 months after therapy, & presence of therapy-related ARs were taken retrospectively from the patients directly, their relatives, seizure diaries or medical record files. These clinical data were used to categorise the predominant seizure type as focal or generalised, in agreement with the International League Against Epilepsy classification of epileptic seizures & epileptic syndromes [13,14]. All the patients underwent several routine investigations including electroencephalography (EEG), brain Magnetic resonance imaging (MRI), complete blood count (CBC), liver function test, & thyroid function test. All patients were informed about the purpose of the study & a written consent was taken before enrolment.

Patients grouping

The study included 75 epileptic patients treated with either LEV or TPM, who were titrated to an individual optimal dosage, & the patients were not limited by age, epilepsy syndrome, or seizure type. For data analysis the patients were divided into two core groups, topiramate (TPM) treatment group (n=30), & levetiracetam (LEV) treatment group (n=45). Each treatment group is then divided according to the type of therapy into monotherapy & add-on therapy groups. Within each, they further subdivided into generalised or focal seizure subgroup.

Inclusion & exclusion criteria

Inclusion criteria included patients who had a clinical diagnosis of epilepsy either generalized (idiopathic primary generalized & myoclonic) or focal (from any cause symptomatic or idiopathic) & continuous on the new therapy for at least six months.

Exclusion criteria included any patients who were intermittently noncompliant with their treatment or clinic follow-up attendances, those who did not document their seizures appropriately [15], patients with absences epilepsy & pregnant females.

Evaluation of AEDs efficacy

Treatment efficacy was evaluated as the percentage of reduction of monthly seizure frequency over six months of treatment & compared to seizure frequency in the last six months before initiation of LEV or TPM. The degree of response was graded as following [13]:

1. Complete seizure freedom: with 100% seizure reduction.
2. Good response: with 50-99% seizure reduction.
3. Minimal response: with 20-50% reduction.
4. Unmodified response: with less than 20% reduction [16].

Evaluation of medication's safety

All patients had been evaluated after six months of therapy for the presence of any drug related ARs like a headache, nervousness, weight gain, depression, weight loss, aggression, diarrhoea, cough, nausea &/or vomiting, blood dyscrasia or abnormality in thyroid or liver function.

Statistical analysis

After describing the characteristics of the patients (i.e. Mean ± Standard Deviation "SD" for continuous variables & the percentage of categorical variables), the Kolmogorov-Smirnov test was utilised to assess the standard distribution of the continuous variables. In the comparison of categorical variables, Fisher's

exact test was used. A two-sided p-value of 0.05 was considered statistically significant. Dat a were evaluated by Statistical Package for Social Sciences ‘‘SPSS version 22 for Windows (SPSS Inc. Chicago, IL, USA)’’.

RESULTS:

The study included 75 epileptic patients. The LEV group included 45 patients (32 F/ 13 M) with a mean age of 24.76 years(y), while the TPM group included 30 patients (11 F/ 19 M) with a mean age of 23.8 y. A family history of epilepsy was observed in 17.8% of LEV & 23.3% of TPM groups (Table -1).

Table 1: Patients demographics & characteristics.

	Levetiracetam (LEV)	Topiramate (TPM)
Total no. of patients	45	30
Age (mean ±SD) y	24.76 ± 14.79	23.8 ± 12.75
Age range	3 - 61	2 - 47
Gender (F/M)	32/13	11/19
Family history of:	8(17.8%)	7(23.3%)
Mode of Therapy		
Mono	15 (33.3%)	11 (37.7%)
Add on*	30 (66.7 %)	19 (63.3%)
Type of seizure		
Focal	9 (20.0%)	6 (20.0%)
Generalized	36 (80 %)	24 (80.0%)
MRI abnormalities	4.4%	3.3%
Median duration of epilepsy /year (min. – max.)	2.5 (1-15)	2.5 (1 –15)
Median no. of attack /month before Rx (min. – max.)	8 (0.25 –90)	30 (0.08-120)
Median no. of attack /month after Rx (min. – max.)	0 (0—15)	0.2(0—30)
Median dose of drug mg /day (min- max)	1000 (500–3000)	125.0(50 – 400)

(*) Drugs received included carbamazepine, Na valproate, clonazepam or phenobarbital.

Fifteen patients (33.3%) of LEV group were on monotherapy & 30 patients (66.7%) were on Add-on therapy. Eleven patients (37.7%) of TPM group were on monotherapy & 19 patients (63.3%) were on add-on therapy. Focal seizures were present in 20% of each cluster while generalised seizures were present in 80% of both of them (Table -1). Significant differences between the two groups regarding mode of therapy or type of seizure was not observed (Table -2).

The median duration of epilepsy was around 2.5 years in both groups. The median number of attacks /month was 8 (0.5 – 90) attacks before LEV therapy, & 30 (0.08 – 120) attacks before TPM therapy. The median Dose of LEV was 1000 (500 –3000) mg/day & 125 (50 – 400) mg/ day for TPM (Table -1).

Table 2 : Shows the number of the patients & type of seizure in each therapy group according to the kind of medication.

P- value[a]	Type of medication		Type of seizure	Type of therapy
	TPM n= 30(100%)	LEV n=45 (100%)		
0.7	9 (37.5%)	12 (33.3%)	Generalized	Monotherapy
	2(33.3%)	3 (33.3%)	Focal	
	15(62.5%)	24(66.7%)	Generalized	Add-on Therapy
	4(66.7%)	6 (66.7%)	Focal	

[a] P-value calculated using Fisher’s exact test

Efficacy

LEV show higher efficacy in overall seizure control than TPM although the difference did not reach a statistically significant level (p-value = 0.1) (Table -3).

Table 3: Compares the efficacy of LEV vs. TPM according to the grade of response in both samples.

P - value[a]	TPM n= 30 (100%)	LEV n=45 (100%)	Grade of response In total samples
0.1	13 (43.3)	26 (57.8)	Seizure Free
	14 (46.7)	19(42.2)	Good Response
	2 (6.7)	0 (0.0)	Minimal response
	1 (3.3)	0 (0.0)	Unmodified response

[a] P-value calculated using Fisher's exact test

The seizure freedom target was achieved in 57.8% of LEV-treated patients vs. 43.8% of TPM-treated patients. The responder rate (≥ 50% reduction in seizure frequency) was 100% with LEV while with TPM it was 90% (Table -3 & Figure 1).

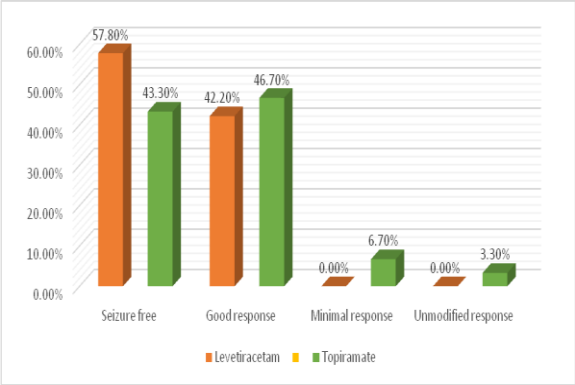

Figure 1: Compares the efficacy of LEV vs. TPM according to the grade of response in both samples.

Both LEV & TPM showed high efficacy in generalised & focal seizures in both add on & monotherapy groups. A greater degree of seizure freedom (83.3%) was noticed with LEV in monotherapy for generalised seizure, vs. 55.6% with TPM monotherapy. For focal seizure, LEV shows the highest difference in efficacy (i.e. ≥ 50% reduction in seizure frequency) against TPM (100% vs. 50% respectively) in both mono & add-on therapy. Despite the above observations none of the two AEDs shows statistically significant superiority over the other in the treatment of epilepsy as monotherapy or add-on therapy in the overall comparison between them (Table -4).

Table 4: Compares the efficacy of LEV vs. TPM in mono & add-on therapy according to seizure types.

P – value[a]	TPM n= 30(%)	LEV n=45(%)	Grade of response	Type of Seizure	Type of medication
0.1	5 (55.6)	10 (83.3)	Seizure Free	Generalized	Mono-therapy
	4 (44.4)	2 (16.7)	Good Response		
	0 (0.0)	0 (0.0)	Minimal response		
	0 (0.0)	0 (0.0)	Unmodified		
	0 (0.0)	2(66.7)	Seizure Free	Focal	
	1 (50.0)	1 (33.3)	Good Response		
	1 (50.0)	0 (0.0)	Minimal response		
	0 (0.0)	0 (0.0)	Unmodified		
	7 (46.7)	11 (45.8)	Seizure Free	Generalized	Add on therapy
	8 (53.3)	13 (54.2)	Good Response		
	0 (0.0)	0 (0.0)	Minimal response		
	0 (0.0)	0 (0.0)	Unmodified		
	1 (25.0)	3 (50.0)	Seizure Free	Focal	
	1 (25.0)	3 (50.0)	Good Response		
	1 (25.0)	0 (0.0)	Minimal response		
	1 (25.0)	0 (0.0)	Unmodified		

[a] P-value calculated using fisher's exact test

No significant difference observed in the efficacy of LEV vs. TPM in the treatment of paediatric or adult patients. There was a non-significant higher degree of seizure freedom with LEV vs. TPM therapy in both age groups, 55% vs. 44% in children & 60% vs. 42% in adults (Table -5).

Table 5: Compares the efficacy of LEV vs. TPM in adults & children according to response.

P – value[a]	TPM n=30(%)	LEV n=45(%)	Grade of response	Age
0.1	4 (44.4)	11 (55.0)	Seizure free	≤18 years old
	4 (44.4)	9 (45.0)	Good response	
	1 (11.1)	0 (0.0)	Minimum response	
	0 (0.0)	0 (0.0)	Unmodified response	
	9 (42.9)	15 (60.0)	Seizure free	>18 years old
	10 (47.6)	10 (40.0)	Good response	
	1 (4.8)	0 (0.0)	Minimum response	
	1(4.8)	0 (0.0)	Unmodified response	

[a] P-value calculated using Fisher's exact test

Regarding the efficacy of low doses LEV vs. small doses of TPM in the total samples, the difference was not significant (p-value = 0.2). Also, no significant difference was seen in the efficacy of high doses LEV vs. high doses of TPM in the total samples. (Table -6)

Table 6: Compares the efficacy of low doses & high doses LEV vs. TPM according to response.

P – value[a]	TPM n=30(%)	LEV n=45(%)	Grade of response	Dose
0.1	11 (42.3)	18 (58.1)	Seizure free	Low dose[b]
	12 (46.2)	13 (41.9)	Good response	
	2 (7.7)	0 (0.0)	Minimum response	
	1 (3.8)	0 (0.0)	Unmodified response	
	2 (50.0)	8 (57.1)	Seizure free	High dose[c]
	2 (50.0)	6 (42.9)	Good response	
	0 (0.0)	0 (0.0)	Minimum response	
	0 (0.0)	0 (0.0)	Unmodified response	

[a] *P-value calculated using Fisher's exact test*

[b] ≤ 1000 mg for LEV & ≤100 mg for TPM

[c] > 1000 mg for LEV & >100 mg for TPM

Safety

Many ARs were reported in both groups, but none of them was so severe to push the patients to stop the AEDs. Both of them have reasonable safety profile. All the reported ARs were clearly

higher in TPM group apart from weight gain & aggression that were more predominant in LEV group. A headache, drowsiness, nervousness were the most common ARs with LVE that affect more than 20% of users. These three ARs were also more frequent with TPM affecting 26-30% of the users, in addition to depression & weight loss that affect 20% of patients on TPM. (Table -7 & Figure -2).

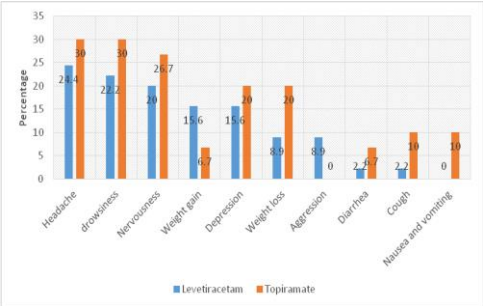

Figure 2: The commonest ARs in each therapy group.

There were no reported significant metabolic abnormalities in any of the two groups. Only one patient on LEV developed minor thyroid function abnormality & 1 patient on TPM developed minor CBC abnormality (Table -7).

Table 7: The commonest ARs in each therapy group [a].

TPM n= 30(100%)	LEV n=45(100%)	ARs
9 (30.0)	11 (24.4)	Headache
9 (30.0)	10 (22.2)	Drowsiness
8 (26.7)	9 (20.0)	Nervousness
2 (6.7)	7 (15.6)	Weight gain
6 (20.0)	7 (15.6)	Depression
6 (20.0)	4 (8.9)	Weight loss
0 (0.0)	4 (8.9)	Aggression
2 (6.7)	1 (2.2)	Diarrhea
3 (10.0)	1 (2.2)	Cough
3 (10.0)	0 (0.0)	Nausea &/or vomiting
1(3.3)	0(0.0)	CBC abnormalities
0(0.0)	1(2.2)	Thyroid function abnormalities

[a] Some of our patients reported more than one side effect.

DISCUSSION:

The goal of present study is to provide neurologists with a helpful information for choice among new AEDs concerning efficacy & treatment safety after long use since successful treatment should balance between obtaining adequate seizure control & avoiding ARs [(4)]. The importance of this study is the direct comparison made between two widely used new AEDs (TPM & LEV) in a single neurology centre. The relatively long period of evaluation & inclusion of both focal and generalized epilepsy resulted in a low risk of selection bias. There was no age or dose limitation. Also, the two studied groups were comparable regarding age, mode of therapy, type of seizure & duration of epilepsy. After six months of treatment, LEV showed a higher efficacy in overall seizure control than TPM, although the difference did not reach a significant level. This result was in accordance with some reported studies[(3,5,17)], while a study by Zaccara et al. concluded different result in which LEV was more effective than TPM [(18)]. Although the difference was not statistically significant both LEV & TPM, showed higher efficacy in generalised seizure rather than focal seizure in both add-on & monotherapy groups. This result was in harmony with a study by Coppola et al. [(19)]; however, it doesn't agree with a study by Lagae et al. who concluded that LEV was equally effective for partial & generalised seizures [(13)]. This finding regarding generalised epilepsy, especially in childhood, is interesting since many

childhood epileptic syndromes, & especially the catastrophic epilepsies, are characterised by the presence of generalised seizures [13]. Moreover, no significant difference observed in the efficacy of LEV vs. TPM in the treatment of paediatric or adult patients. There was a non-significant higher degree of seizure freedom with LEV vs. TPM therapy in both age groups, 55% vs. 44% in children & 60% vs. 42% in adults. Other investigators found that increase in patients' age was associated with an increase in the efficacy of TPM while the risk of aggravation decreased significantly [20]. In the present study, 57.8% of the LEV-treated group was seizure free vs. 43.8% of the TPM-treated group. Possibly, this difference is due to a rapid onset of action of LEV; this concept is also supported by a study done by Bootsma et al. [3]. In the present study, there was no statistically significant difference in the term of efficacy when the treatment used as monotherapy or add-on therapy in the overall comparison between the two drugs. However, this result didn't agree with Kholin et al. who concluded that the efficacy of TPM was greater as monotherapy compared to that of add-on therapy [20]. Regarding the ARs, there were many reported ARs in both groups, but none was so severe to push the patients to stop the AEDs after more than six months of use. Both of LEV & TPM had reasonable safety profiles. These results were in harmony with many other studies [2,5,21]. However, the long-term safety profile of LEV was more favourable than TPM. This result was in agreement with Bootsma et al. report that TPM has a higher rate of ARs than LEV leading to more withdrawal than LEV does [3]. The present study enrolled those who were on new AEDs for more than six months for observation of long-term effect & ARs, so the data about those who withdrew their medication due to initial ARs are lacking. This study design also reflected on the responder rate in this work that was higher than many of other published studies, because they enrolled patients from start of therapy including those who stop medication due to lack of efficacy or presence of ARs shortly after initiation. The data in this study reflect real life data of epileptic patient's exposure to different AEDs with different dosages & a wide range of age. Furthermore, the percentage of the females was more than the percentage of males in the LEV-treated group since no teratogenic, mutagenic, or immune toxic effects had associated with LEV administration in studies on several animal species. Therefore LEV was prescribed for most of the female cases [5] . Overall, this study confirmed that LEV & TPM are a broad-spectrum anti-epileptic drug with a favourable safety profile. The effects on behaviour need further quantitative research.

CONCLUSION:

Both LEV & TPM are broad spectrum AEDs. Their efficacies were almost equal in the treatment of focal or generalised seizures as monotherapy or add-on therapy after six month of use. Although LEV showed a higher degree of seizure freedom & responder rate, the difference did not reach a statistically significant level. Both of the drugs were equally effective in adults & paediatric patients, in high & low doses. The safety profile of LEV was more favourable than TPM.

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