



Pediatric Sciences Journal

Published by
Pediatrics Sciences Journal

Comparison efficacy and safety sodium valproate versus combination sodium valproate and levetiracetam for treatment epilepsy in children: a meta-analysis



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ABSTRACT

Background: The most prevalent severe neurological condition, impacting more than 50 million individuals globally, is epilepsy. A new anti-epileptic drug (AED) called levetiracetam (LEV) has shown promise as an adjuvant treatment for children's treatment-resistant partial-onset seizures. Sodium valproate (SV) is a commonly used anti-epileptic medication that has a range of effects and a distinct mode of action. Combining LEV and SV has emerged as a viable clinical treatment plan. This study aimed to use meta-analysis to estimate the safety and effectiveness of LEV with SV in pediatric epilepsy patients.

Methods: From January 1993 to April 2023, the Cochrane Library, PubMed, and ScienceDirect were searched. The included literature consisted of randomized controlled clinical trials that examined the use of SV in conjunction with LEV in pediatric epileptic patients. This meta-analysis followed the PRISMA guidelines. The statistical program used for the meta-analysis was Revman V.5.4.1.

Results: From 568 original titles screened, data were extracted from 3 studies (n=303). Compared with SV alone, SV combined with LEV significantly improved the overall therapeutic effect of epilepsy (OR=0.80; 95%CI= 0.72-0.89; p<0.0001). The observation group significantly reduced the occurrence of adverse drug reactions (ADRs) of nausea and vomiting (OR=2.77; 95%CI=1.08-7.09; p=0.03).

Conclusion: According to this meta-analysis, SV plus LEV considerably increased the overall therapeutic effect of epilepsy while concurrently lowering the incidence of ADRs when compared to SV alone. Thus, for treating epilepsy in children, we advise SV in conjunction with LEV.

Keywords: levetiracetam (LEV), sodium valproate (SV), epilepsy, efficacy, safety, children.

Cite This Article: Gasti, D.R., Hapsari, A.S., Iffani, K. 2023. Comparison efficacy and safety sodium valproate versus combination sodium valproate and levetiracetam for treatment epilepsy in children: a meta-analysis. *Pediatrics Sciences Journal* 4(2): 54-59. DOI: 10.51559/pedscij.v4i2.54

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Received: 2022-09-08

Accepted: 2023-11-12

Published: 2023-12-05

INTRODUCTION

The most prevalent severe neurological condition, impacting more than 50 million individuals globally, is epilepsy.¹ Uncontrolled seizures affect 30% of people, which has been linked to mental disease and a poor quality of life.² The likelihood of having a single epileptic seizure in one's lifetime is 10%. The most frequent causes of seizures in children are hereditary, prenatal damage-related injury, and anomalies of cortical development.³ The International League Against Epilepsy (ILAE) Task Force developed the operational (practical) clinical definition of epilepsy, which is defined as a brain disease indicated by any of the following conditions: one unprovoked (or reflex) seizure and a probability of additional

seizures equal to or greater than the general recurrence risk (at least 60%) following two unprovoked seizures that occur over the following ten years.⁴ Additionally, several studies have shown that youngsters experience epilepsy more frequently than adults.⁵ In the course of epileptogenesis, overexcited neurons in the vicinity of the lesion produce paroxysmal aberrant high-frequency discharges that spread to the surrounding tissue, resulting in rapid, transitory, and recrudescing brain dysfunction.⁶ Pediatric epilepsy frequently results in significant neural damage due to the insufficient development of children's central nervous systems, which may lead to other neurological diseases in children, such as strokes. In the most severe situations, mental retardation can happen, causing significant brain damage

to the kid and adding to the load on the family and society.⁷ There are currently no agreed-upon guidelines for the clinical management of pediatric epilepsy.⁸ Therefore, one of the main therapeutic tasks is to investigate safe and effective therapies for pediatric epilepsy.⁹

Valproate, a first-line broad-spectrum anti-epileptic drug (AED), is believed to offer protection against a range of seizure types.¹⁰ One of the most adaptable and powerful AED is valproate.¹¹ Treatment for absence, myoclonic, partial, and tonic-clonic seizures is successful with valproate.¹² After an oral dose, valproate is effectively absorbed, with bioavailability exceeding 80%. Two hours are needed to see peak blood levels. If a medication is taken after a meal, food may help to increase tolerability and delay absorption.¹³ The

most frequent side effects of valproate that are dose-related include nausea, vomiting, and other gastrointestinal problems such as heartburn and stomach discomfort.¹⁴ To prevent these adverse effects, the medication should be taken gradually. At higher levels, a slight tremor is frequently noticed. Some patients experience reversible side effects, including weight gain, increased hunger, and hair loss. Patients under the age of two and those taking various drugs are most in danger.¹⁵

One of the most commonly suggested treatments for epilepsy is the broad-spectrum AED Levetiracetam (LEV).¹⁶ This is primarily because of its perceived low risk of side effects, wide therapeutic window, excellent pharmacokinetics, and lack of drug-drug interactions.¹⁷ Treatment of myoclonic, partial, and tonic-clonic seizures with LEV is beneficial. 20–40 mg/kg/day of oral maintenance medication for children with therapeutic values of 6–20 mg/L.¹⁸ LEV side effects include drowsiness, asthenia, ataxia, infection (colds), and ataxia.¹⁹ Extended-release pills are one type of oral formulation, and an intravenous preparation is also offered.²⁰

Sodium valproate (SV) is traditionally used to treat epilepsy, although there are worries regarding its adverse effects and teratogenicity. LEV is generally well tolerated and has a substantially lower risk of teratogenicity. LEV is, therefore, now preferred, especially for girls and women, since treatment for epilepsy is frequently ongoing.²¹ Clinical professionals may find this valuable information in light of the previously mentioned statistics and the large number of recent trials. We conducted a systematic review and meta-analysis to compare the efficacy and safety of SV alone vs. SV plus LEV in the treatment of pediatric epilepsy.

METHODS

Literature search

PRISMA recommendations form the basis of our meta-analysis.²² The Cochrane, ScienceDirect, and PubMed search pages were utilized to find the libraries. LEV, SV, epilepsy, and efficacy and safety in treating epilepsy patients in children were included as keywords. All libraries with randomized controlled trials, which covered the period from January 1993 to April 2023, were

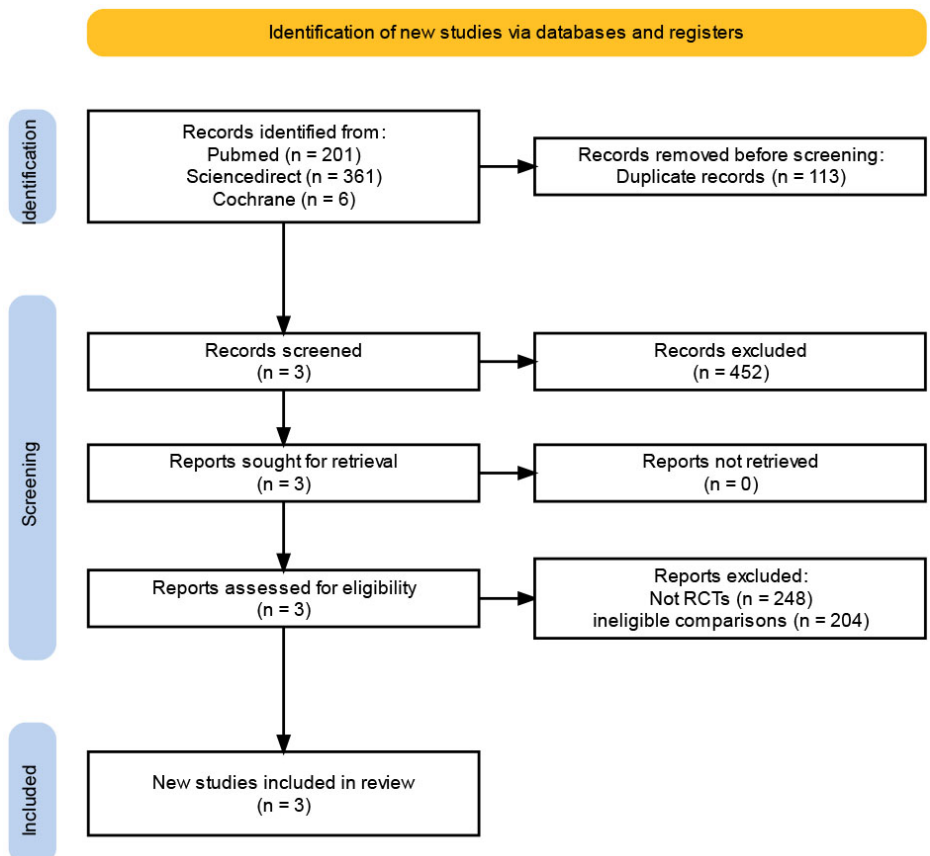


Figure 1. The PRISMA about the study search, selection, and inclusion process.

included in the search, presented in [Figure 1](#).

Inclusion and exclusion criteria

The inclusion characters of the articles used in this analysis were (1) randomized control trials (RCTs), (2) a combination of LEV and SV, and (3) the article at least includes the results of reducing adverse drug reactions. References will be excluded if the article is an editorial, case report, or review article, and all references other than RCTs; Libraries that do not report the results of the adverse drug reactions of the combination of LEV and SV; data that are incompatible and cannot be extracted/processed are also excluded. The author did the screening readings, pulled the data, and collected all the results and side effects of the drugs.

Outcome assessed

The effectiveness of the combination of LEV and SV in treating children with epilepsy was one of the parameters we observed, as was the safety of the combination in decreasing side effects.

Assessment of study quality

We used the Jadad score, an evaluation of the Jadad score based on accessible criteria from studies at the Oxford Center for Evidence-Based Medicines, to determine the quality of the publications that satisfied the inclusion criteria. The article is considered good quality if the value is greater than 4. The score ranges from 0 to 5. A study with a 3–4 score is considered average quality. When the score is less than 3, it is considered low quality.²³

Statistical analysis

Review Manager version 5.4.1 is used in this study's statistical analysis. The odds ratio is computed using a 95% confidence interval (CI) because the data measurement is dichotomous (OR). We also calculated the heterogeneity distribution in each trial using the Cochrane Chi-Square test and inconsistency (I^2); if the p-value is less than 0.05, it is considered significant. The study's heterogeneity is substantial if the inconsistency value (i^2) is > 50%.

Table 1. Characteristics of study quality and articles

Article	Intervention	Country	Study Design	LE	Jadad Score	Case (n)	
						SV	Combination SV and LEV
Chen 2021	SV vs. combination SV and LEV	China	RCT	1b	3	40	43
Liu 2019	SV vs. combination SV and LEV	China	RCT	1b	3	50	50
Zhao 2019	SV vs. combination SV and LEV	China	RCT	1b	3	60	60

LE: Level of Evidence Base; RCT: Randomized Control Trial



Figure 2. Forest plots of the efficacy based on RR for overall therapeutic effect.

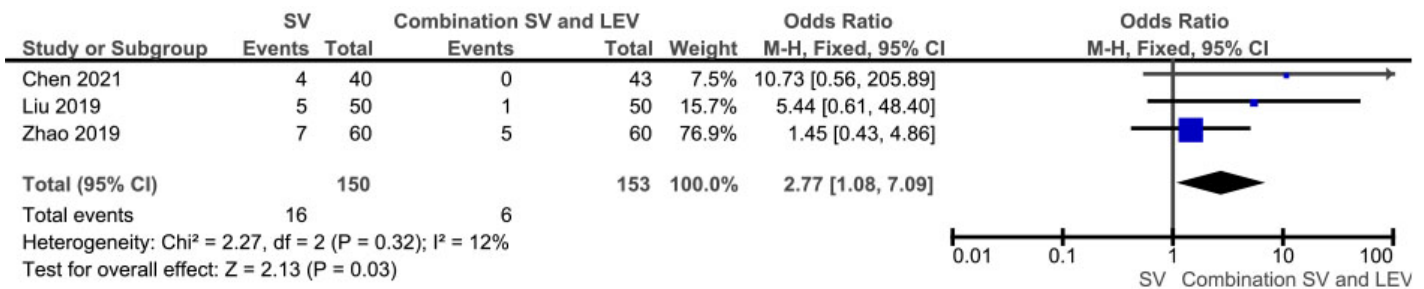


Figure 3. Forest plots of the efficacy and safety of a combination of SV and LEV based on OR for ADR nausea and vomiting.

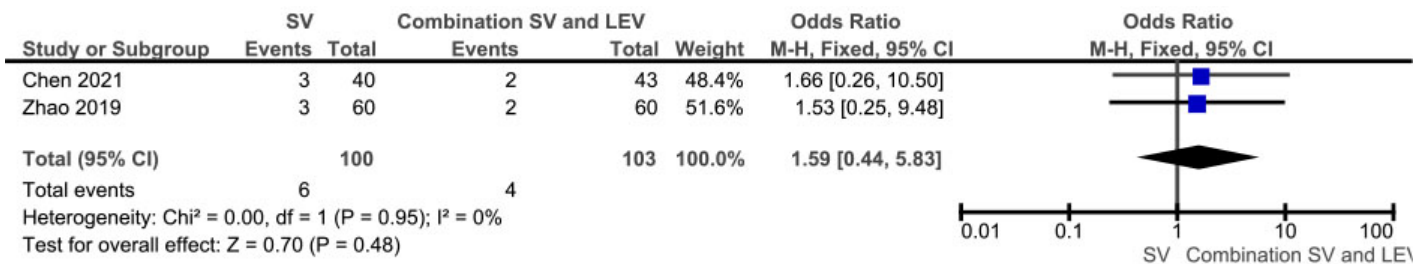


Figure 4. Forest plots of the efficacy and safety of a combination of SV and LEV based on OR for ADR dizziness.

RESULTS

Literature screening process and results

We identified 568 possibly relevant studies. Three trials met the prospective inclusion criteria and were included in our meta-analysis.

Study characteristics

A total of 303 patients were included in three studies. All of the studies were published in 2019 and 2021. For these studies, 40 was the minimum,

and 60 was the maximum number of participants. Only SV was administered as the control group in one of the three RCTs; the other two used either SV or SV plus topiramate.^{24,25,26} With regard to interventions, all 3 RCTs combined SV with LEV. The characteristics of each study are shown in Table 1.

Efficacy therapeutic effect

Data on the overall therapeutic effect were provided by all three trials (n = 303). The application of SV combined with LEV in the treatment of pediatric epilepsy

significantly improved the efficacy therapeutic effect (OR=0.80; 95%CI=0.72-0.89; p < 0.0001) with high heterogeneity I²=12%, as compared with SV alone or SV combined with topiramate. Figure 2 illustrates this finding.

Adverse event

Nausea and Vomiting

Three studies reported decreasing side effects of nausea in combination with SV and LEV (OR=2.77; 95%CI=1.08-7.09; p=0.03) with high heterogeneity I²=12%, as shown in Figure 3.

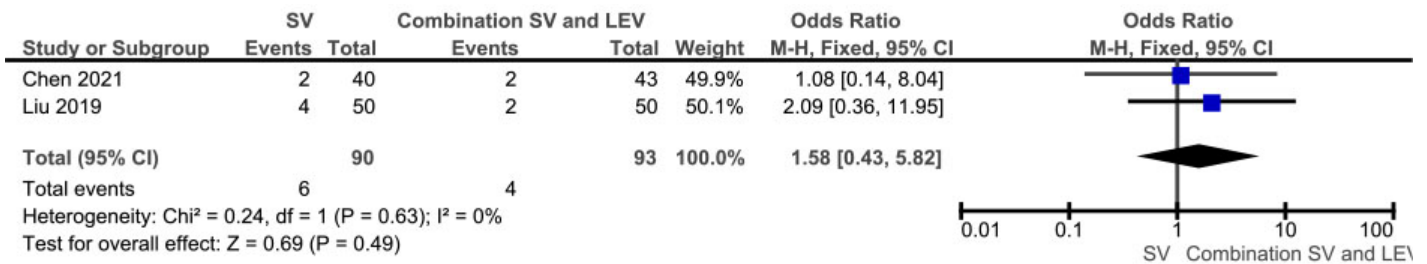


Figure 5. Forest plots of the efficacy and safety of combination SV and LEV based on OR for ADR diarrhea and gastrointestinal reactions.

Dizziness

In two studies in pooled analysis with 100 patients in the SV group and 103 patients in combination SV and LEV group, no significant difference was reported (OR=1.59; 95%CI=0.44-5.83; p=0.48) with no heterogeneity I²=0% mis shown in Figure 4.

Diarrhea and Gastrointestinal Reaction

Investigators reported a gastrointestinal tract problem and diarrhea in two studies, showing no significant difference (OR=1.58; 95%CI=0.43-5.82; p=0.49) with no heterogeneity I²=0%, as shown in Figure 5.

DISCUSSION

Epilepsy is a problem in developing nations.²⁷ One of the chronic brain problems that affects people of all ages, including children, is epilepsy. Although the AED can be prescribed alone (monotherapy) or in combination with other medications (polytherapy), using a single medication is generally advised when treating epilepsy when considering the risk-benefit ratio in patients, especially in pediatrics.²⁸ Asia is home to more than half of the 50 million epileptics worldwide, according to estimates.²⁹ One of the most prevalent neurological conditions in Indonesia, particularly in young children under the age of five.³⁰ A neurological condition known as epilepsy is brought on by irregular brain nerve activity that results in recurrent seizures.³¹ The incidence is 114 per 100,000 people annually. In contrast to industrialized nations, there are between 24 and 53 incidences of epilepsy per 100,000 people per year in poor nations.³²

One of the most often prescribed AEDs in clinical practice is SV, a broad-spectrum,

highly selective agent.³³ However, if SV is the only medication used, it might be challenging to control the condition completely.³⁴ Meanwhile, the liver breaks down SV, potentially harming a child's liver function.³⁵ Additionally, the anti-seizure treatment process is challenging, and several side effects tend to exacerbate the pain of the medication, decreasing children's adherence to the medication and producing unsatisfactory results.³⁶

One of the most promising anti-seizure medications is LEV, which also has an excellent pharmacokinetic profile, few drug interactions, and a novel mechanism of action.³⁷ An entirely unique mechanism for LEV's action has never been mentioned in any other anti-seizure medication.³⁸ Recent preclinical studies suggest that LEV, especially when combined with SV, may have an extra therapeutic advantage due to its enhanced protective function.³⁹ Compared to all other clinically used combinations of anti-seizure medications, LEV shows a clear and significant enhancement of the anticonvulsant effect of SV.⁴⁰

In contrast to SV alone or SV combined with topiramate, the application of SV combined with LEV in the treatment of childhood epilepsy can significantly improve the efficacy of therapeutic effects while at the same time reducing the occurrence of adverse reactions, according to the findings of this meta-analysis.²⁴ LEV and SV together show that these two broad-spectrum epilepsy medications do not increase patients' sensitivity to them but rather increase their effectiveness.⁴¹

A critical review of several preclinical trials involving levetiracetam and other anticonvulsants in combination therapy for different seizure and epilepsy models is presented in this report. Levetiracetam

typically amplifies the protective effects of a wide range of clinically used AEDs or other anticonvulsants; valproate was a particularly popular AED in this context.⁴² Different drug doses, combinations, and inter-individual variability can all affect blood drug levels. In order to ensure that the blood level of the medication is within the therapeutic range, the dosage setting and frequency of administration must be taken into account. The medicine often will not have a therapeutic impact if levels are below the minimally adequate level. Contrarily, drug toxicity symptoms typically manifest if the drug's level in the blood surpasses the lowest toxicity limit. Combinations in the therapeutic regimen can also significantly affect drug levels.⁴³ Conversely, levetiracetam and valproate combinations significantly raised the therapeutic index, calculated as the difference between the toxic dose of 50% (TD₅₀) and the effective dose of 50% (ED₅₀). Additionally, when levetiracetam was observed to enhance the anticonvulsant effects of other medications, the therapeutic index was significantly higher. Levetiracetam was administered concurrently with plasma and brain AED concentrations. However, this had no effect. The lone exception was SV, but its plasma and brain concentrations were decreased when levetiracetam was also administered.⁴² This combination is more effective and reduces the side effects of nausea and vomiting due to the lowered plasma and brain concentrations.

Furthermore, according to two studies, using LEV and SV together can lessen patients' symptoms of nausea and vomiting; other studies also explained that the combination of valproic acid and LEV reduced the side effects of nausea and vomiting.⁴⁴ Based on the data above,

nausea and vomiting can significantly decrease when SV is combined with LEV.

There are some limitations in this study. First, only three RCTs were included; additional RCTs are needed to confirm our findings. Second, the outcomes of the included trials were not all the same, but the clinical efficacy was significant enough to compare the relative superiority of the therapy. Finally, due to the small sample and race of the individuals, it may not have been able to identify significant differences across the various groups.

CONCLUSION

This meta-analysis study demonstrated the combination of SV and LEV to be significantly effective. Nausea and vomiting are side effects that have diminished when SV and LEV are combined.

ETHICAL APPROVAL

Not applicable.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

FUNDING

None.

AUTHOR CONTRIBUTIONS

DR: concepts, design, definition of intellectual content, literature search, data analysis, statistical analysis, manuscript preparation, manuscript editing, manuscript review, guarantor. AS: data analysis, statistical analysis, manuscript editing. KI: definition of intellectual content, literature search, manuscript preparation, manuscript editing.

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