ARTÍCULO DE REVISIÓN

Refractory Infantile Spasm Syndrome Treatment: A Systematic Review

Tratamiento del Síndrome de Espasmos Infantiles Refractario: Una Revisión Sistemática

Ruth Elizabeth Chávez-Nomberto,[1] Manuel André Virú-Loza,[2] Adrian V. Hernandez[2]

Abstract

Introduction: Infantile spasm syndrome is an epileptic and neurodevelopmental encephalopathy whose first-line treatment includes vigabatrin and hormonal therapy. However, there are refractory cases.

Objective: To compare the efficacy of the available treatments for refractory infantile spasm syndrome (RISS).

Methods: We searched PubMed, Embase, Scopus, Web of Science, Cochrane CENTRAL Clinical Trials, International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov until March 2024 for randomized controlled trials (RCTs) comparing the efficacy of two of the following three treatment alternatives: antiepileptics, ketogenic diet and surgery. The primary outcome was electroclinical response. The GRADE methodology was used to appraise the certainty of the evidence. We generated a Summary of Findings table using the GRADEpro software.

Results: We did not find enough RCTs to do a meta-analysis. Only one trial was close to fulfill our inclusion criteria. This study involved 318 patients with RISS receiving antiepileptic drugs and compared the modified Atkins diet (MAD) versus normal diet. However, we found a high risk of bias.

Conclusion: High-quality RCTs comparing treatment modalities for patients with RISS are urgent due to the devastating nature of this condition.

Keywords: Infantile Spasms, Epilepsy, Epileptic Syndromes, Central Nervous System, Systematic Review

Resumen

Introducción: El síndrome de espasmos infantiles es una encefalopatía epiléptica y del neurodesarrollo cuyo tratamiento de primera línea incluye vigabatrina y terapia hormonal. Sin embargo, hay casos refractarios.

Objetivo: Comparar la eficacia de los tratamientos para el síndrome de espasmos infantiles refractarios (SEIR).

Metodología: Se realizaron búsquedas en PubMed, Embase, Scopus, Web of Science, Cochrane CENTRAL Clinical Trials, International Clinical Trials Registry Platform (ICTRP) y ClinicalTrials.gov hasta marzo de 2024 para encontrar ensayos controlados aleatorizados (ECAs) que compararan la eficacia de dos de las siguientes tres alternativas de tratamiento: antiepilépticos, dieta cetogénica y cirugía. El resultado primario fue la respuesta electroclínica. Se utilizó la metodología GRADE para valorar la certeza de la evidencia. Generamos una tabla Resumen de Hallazgos utilizando el software GRADEpro.

Resultados: No se encontraron suficientes ECAs para realizar un meta-análisis. Sólo un ensayo estuvo cerca de cumplir los criterios de inclusión. En dicho estudio participaron 318 pacientes con SEIR que recibían fármacos antiepilépticos y se comparó la dieta Atkins modificada (DAM) con la dieta normal. Sin embargo, encontramos un alto riesgo de sesgo.

Conclusión: Urgen ECAs de calidad que comparen las modalidades de tratamiento para pacientes con SEIR dada la naturaleza devastadora de esta afección.

Palabras clave: Espasmos Infantiles, Epilepsia, Síndromes Epilépticos, Sistema Nervioso Central, Revisión Sistemática

Rev. Ecuat. Neurol. Vol. 35, N° 1, 2026

Introduction

Infantile spasm syndrome is a developmental and epileptic encephalopathy that begins in childhood.[1,2]

Infantile spasms are epileptic seizures characterized by abrupt and short contractions of the neck, trunk, and extremities muscles, usually lasting less than 1 second to 1 – 2 s and occurring in clusters.[2] First-line treatment includes vigabatrin and hormone therapy (with ACTH or prednisolone), either alone or in combination.[1,3-6] However, some patients are refractory to first-line treatment, which accounts for approximately 30 to 50% of cases.[3,4,7,8] Many alternatives have been proposed

[1]Departamento de Pediatría, Hospital Nacional San Bartolomé, Lima, Perú.
[2]Unidad de Revisiones Sistemáticas y Meta-análisis, Vicerrectorado de Investigación, Universidad San Ignacio de Loyola, Lima, Perú.

Correspondencia:
Manuel André Virú-Loza
Address: Av. La Fontana 550, La Molina, 00012 Lima, Perú.
E-mail: mviru@usil.edu.pe

in these refractory cases, including different antiepileptics, ketogenic diet, and epilepsy surgery.[1] Nevertheless, there is no consensus on the best way to treat refractory infantile spasm syndrome (RISS).

There have been previous systematic reviews about infantile spasms treatment.[9-16] However, they have not focused on cases refractory to first-line treatment or RISS.

Since there is a gap in the literature and a lack of consensus on the treatment of RISS, and we have not found systematic reviews addressing the treatment of RISS as a separate entity, this systematic review aimed to compare the efficacy of the available treatments for RISS.

Methods

This study was a systematic review, and its initial protocol has been appropriately registered in PROSPERO (CRD42023400914). To increase the scope of our systematic review, we broadened the population of our initial protocol from children with refractory West syndrome to patients with RISS. Our systematic review was reported according to the PRISMA 2020 guidelines.[17]

Study searches

We searched the following electronic databases: PubMed, Embase, Scopus, Web of Science, Cochrane CENTRAL Clinical Trials (Through OVID), International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov (Table 1). The search was conducted from database inception until March 05, 2024. There were no restrictions on publication dates. We selected articles in English or Spanish. We also conducted a hand search of lists of citations for all the articles that were included and for relevant review articles to find studies that could be eligible.

Study selection

We included only randomized controlled trials (RCTs) comparing the effect of two of the following three interventions: antiepileptic medications, ketogenic diet and epilepsy surgery, in children with RISS. We defined RISS as ISS that fails to respond or relapses after first-line therapy (hormonal therapy or vigabatrin). The primary outcome we looked for was electroclinical response, and secondary outcomes were spasm freedom, resolution of hypsarrhythmia, and seizure reduction. Electroclinical response was defined as the cessation of infantile spasms coupled with resolution of hypsarrhytmia on the electroencephalogram.

We uploaded all references (titles and abstracts) from the electronic search to EndNote 20 and used the duplicate search tool to automatically find and delete duplicate records. After this, we uploaded the remaining references to Rayyan (https://www.rayyan.ai/). After identifying more duplicate records with the Rayyan's duplicate search tool and removing again duplicate records after a manual review of the duplicates identified, the remaining titles and abstracts were independently screened by two authors (M.V. and R.C.) to identify relevant studies. Afterwards, the same authors (M.V. and R.C.) independently examined the full texts of selected studies to verify inclusion criteria. Disagreements on title/abstract and full-text selection were resolved by discussion.

Data extraction

After the final selection of articles, two authors (M.V. and R.C.) independently extracted relevant data using a standardized form in an Excel spreadsheet. This spreadsheet had been tested prior to use. Data extracted included the following: sample size, country, study

Table 1. Search strategies.

Database	Search Strategy
Pubmed	("west syndrome"[tiab] OR "west syndrome"[tw] OR "Spasms, Infantile"[mesh] OR "infantile spasms" [tiab] OR "infantile spasms" [tw] OR "epileptic spasms"[tiab] OR "epileptic spasms"[tw]) AND (anticonvuls*[tiab] OR antiepileptic*[tiab] OR anticonvuls*[tw] OR antiepileptic*[tw] OR "Anticonvulsants"[mesh] OR callosotomy[tiab] OR surg*[tiab] OR operat*[tiab] OR callosotomy[tw] OR surg*[tw] OR operat*[tw] OR "Surgical Procedures, Operative"[mesh] OR "ketogenic diet"[tiab] OR "ketogenic diets"[tiab] OR "ketogenic diet"[tw] OR "ketogenic diets"[tw] OR "Diet, Ketogenic"[mesh])
Embase	('infantile spasm'/exp OR 'infantile spasm' OR 'west syndrome'/exp OR 'west syndrome') AND ('anticonvulsive agent'/exp OR 'anticonvulsive agent' OR 'ketogenic diet'/exp OR 'ketogenic diet' OR 'ketogenic diets' OR anticonvuls* OR antiepileptic* OR surg* OR operat* OR 'callosotomy')
Scopus	TITLE-ABS-KEY ("west syndrome" OR "epileptic spasms" OR "infantile epileptic spasm syndrome" OR "infantile spasms") AND (anticonvuls* OR antiepileptic* OR surg* OR operat* OR "callosotomy" OR "ketogenic diet" OR "ketogenic diets")
Web of Science	ALL = ("west syndrome" OR "epileptic spasms" OR "infantile epileptic spasm syndrome" OR "infantile spasms") AND (anticonvuls* OR antiepileptic* OR surg* OR operat* OR "callosotomy" OR "ketogenic diet" OR "ketogenic diets")
Cochrane CENTRAL Clinical Trials (Through OVID)	(infantile spasms OR west syndrome OR epileptic spasms OR infantile epileptic spasms OR infantile epileptic spasms syndrome) AND (anticonvulsant* OR antiepileptic* OR anticonvulsive* OR surgery OR callosotomy OR ketogenic diet) {Including related terms}
International Clinical Trials Registry Platform (ICTRP)	(infantile spasms OR west syndrome OR epileptic spasms OR infantile epileptic spasms OR infantile epileptic spasms syndrome) AND (anticonvulsant* OR antiepileptic* OR anticonvulsive* OR surgery OR callosotomy OR ketogenic diet)
ClinicalTrials.gov	Condition/disease: "Infantile Spasms" OR "West Syndrome" Intervention/treatment: Anticonvulsants OR Surgery OR "Ketogenic diet"

design, inclusion criteria, study treatment, comparator, and outcomes per study arm. Any disagreements were solved by discussion.

Risk of bias assessment

We assessed the risk of bias using the Cochrane Risk-of-Bias 2.0 tool for RCTs (RoB2).[18] Two authors (M.V. and R.C.) independently performed a risk of bias assessment. Any disagreements were solved by discussion. The domains assessed by this tool were five: risk of bias arising from the randomization process, risk of bias due to deviations from the intended interventions (it has two subdomains: effect of assignment and effect of adhering), risk of bias due to missing outcome data, risk of bias in measurement of the outcome and risk of bias in selection of the reported result.[18] Each of the domains is given a category of risk of bias: low, some concerns, or high.[18] Overall risk of bias is equivalent to the higher risk of bias among the domains assessed.[18]

Assessment of the quality of evidence

The certainty of the evidence per outcome was evaluated using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach.[19] The GRADE methodology assesses five items: consistency, risk of bias, indirectness, reporting bias and imprecision.[19] The quality of evidence of each outcome began as high and was decreased based on issues on one or more aspects described above.[19] We used the GRADEpro software (McMaster University and Evidence Prime, 2021; www.gradepro.org/) to create the Summary of Findings (SoF) table.

Results

The flowchart of study selection is presented in Figure 1. A total of 15197 references (titles and abstracts) were initially identified. After duplicate screening, 9469 articles were excluded. Then, through careful screening of the remaining titles and abstracts for relevant studies, 5376 articles were also excluded. Subsequently, the remaining 352 articles underwent a thorough full-text evaluation. Ultimately, only the article by Sharma et al. was close to meet our inclusion criteria.[20] Thus, no meta-analysis was performed.

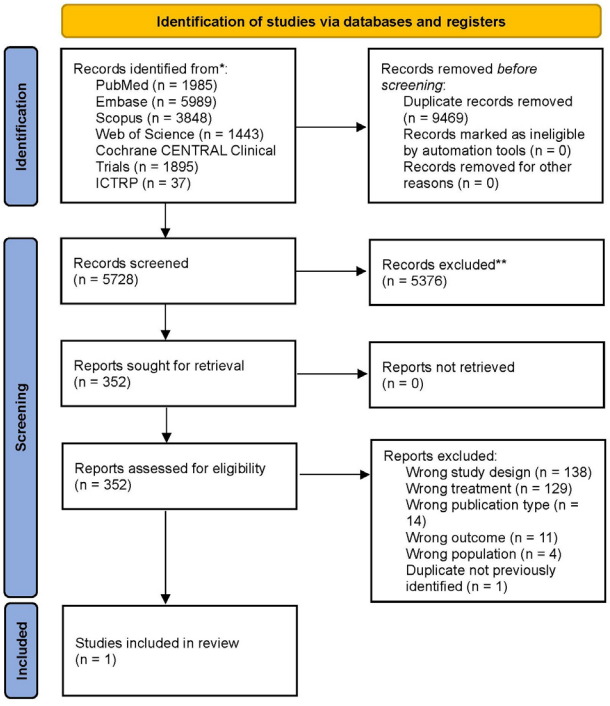

Figure 1. Study selection flow diagram.

The RCT by Sharma et al. included 91 children aged 9 to 36 months having daily spasms for at least 4 weeks and hypsarrhythmia or its variants on EEG, despite receiving previously ACTH or oral prednisolone and one additional antiepileptic medication (vigabatrin, sodium valproate, topiramate, zonisamide, levetiracetam or benzodiazepines).[20] The study by Sharma et al. compared the effect of the modified Atkins diet (MAD) versus normal diet (both groups remained on the same ongoing anticonvulsant medication unless a change in the medication was medically indicated).[20] Thus, this study compared the effect of MAD and antiepileptics versus anticonvulsant medications alone in children with RISS. Its primary outcome was the proportion of children who achieved spasm freedom as per parental reports at 4 weeks.[20] Secondary outcomes were time to spasm cessation, proportion of children with electroclinical remission, proportion of children with > 50% reduction of spasms at 4 weeks as compared to baseline, and adverse effects of the diet (Table 2).[20]

Table 2. Characteristics of the study included in this review.[20]

Study	Sample size	Country	Study Design	Inclusion criteria	Study Treatment	Comparator	Outcomes
Sharma et al. (2021)	91	India	Randomized controlled trial	Age 9-36 months. Daily infantile spasms for at least 4 weeks. EEG of hypsarrhythmia or its variants despite a trial of ACTH or oral prednisolone and 1 additional antiepileptic drug	Modified Atkins diet	Normal diet	Primary outcome: Proportion of children who achieved spasm freedom as per parental reports at 4 weeks. Secondary outcomes: Time to spasm cessation, proportion of children with electroclinical remission, the proportion of children > 50% reduction of spasms at 4 weeks as compared to baseline, and adverse effects of the diet.

After risk of bias assessment, we concluded that the study by Sharma et al. had a high risk of bias related to measurement of the outcome (Table 3). Further, according to the GRADE approach, we concluded that all outcomes had a very low quality of evidence related to serious risks of bias and imprecision (Table 4).

Discussion

We did not find enough RCTs to perform a meta-analysis to compare the efficacy of anti-epileptics, ketogenic diet and surgery for RISS. We only found one trial comparing ketogenic diet versus anti-epileptics.[20] Thus, in children with RISS, there is a lack of high-quality evidence to answer which is the best medical therapy between the three treatment alternatives.

To date, the potential pharmacological therapies for RISS include pharmacological and non-pharmacological alternatives, such as ketogenic dietary therapies and epilepsy surgery.[1]

Several studies have assessed the effect of pharmacological therapies for RISS. For example, the effect of levetiracetam at a dose of 20 mg/kg/day was assessed in a small study of seven patients with RISS[21] that showed a spasm reduction rate of 75% but only in two patients.[21] Further, topiramate has shown conflicting results either as monotherapy or as an adjunct for treating West syndrome, with a long-term response rate in children refractory to first-line treatment of only 5%.[22] Moreover, an open-label randomized trial assessed the effectiveness of topiramate and levetiracetam alone or combined in 20 patients with RISS did not show better results.[23] At four weeks of therapy, patients who did not respond to either drug were subsequently crossed over to the other drug without a washout period.[23] This trial showed that two patients successfully responded to monotherapy, but none of the rest responded to either monotherapy or combined therapy.[23] Additionally, the effect of clobazam in patients with RISS was also assessed in a retrospective study that included 171 patients.[24] In this study, a ≥50% seizure frequency reduction was achieved in 60.2% of patients, with a 22.2% complete response rate.[24]

There are also studies assessing the effect of some antiepileptics specifically in patients with West syndrome refractory to first-line therapy. In these patients, studies show a 0-75% spasm-free rate after using felbamate.[25] However, they are non-controlled retrospective studies and show a wide response rate variation, making them unsuitable for giving an evidence-based recommendation.[25] Moreover, cannabidiol does not seem to be an effective option either since there is a study that showed only one of nine patients that failed treatment with both adrenocorticotropic hormone (ACTH) and vigabatrin (VGB) responded to this treatment.[26] Still, the response was only temporary.[26] Further, the use of zonisamide has shown poor results. In a study of 78 patients there was no clinical or electroclinical response.[27] In fact, a prospective observational study showed that non-standard therapies such as zonisamide were inferior to hor-

Table 3. Risk of bias assessment results using the Cochrane Risk-of-Bias 2.0 tool for randomized trials (RoB2).[20]

Study	Domains	Risk of Bias
Sharma et al. (2021)	Risk of bias arising from the randomization process	Low
	Risk of bias due to deviations from the intended interventions (effect of assignment)	Some concerns
	Risk of bias due to deviations from the intended interventions (effect of adhering)	High
	Risk of bias due to missing outcome data	Low
	Risk of bias in measurement of the outcome	High
	Risk of bias in selection of the reported result	Low
	Overall risk of bias	High

Table 4. Summary of findings table of the quality of evidence per outcome.

	N° of patients			Certainty assessment						
Outcome	MAD	AE	Effect	Nº studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Certainty
Electroclinical resolution at 4 weeks	9/46 (19.6%)	0/45 (0.0%)	NE*	1	Serious[a]	Not serious	Not serious[b]	Serious[c]	Publication bias strongly suspected[d]	⊕○○○ Very low
Spasm free at 4 weeks	11/46 (23.9%)	0/45 (0.0%)	NE*	1	Serious[a]	Not serious	Not serious[b]	Serious[c]	Publication bias strongly suspected[d]	⊕○○○ Very low
50% reduction in spasms at 4 weeks	30/46 (65.2%)	0/45 (0.0%)	NE*	1	Serious[a]	Not serious	Not serious[b]	Serious[c]	Publication bias strongly suspected[d]	⊕○○○ Very low
Days to achieve spasm cessation	46	45	NE**	1	Serious[a]	Not serious	Not serious[b]	Serious[c]	Publication bias strongly suspected[d]	⊕○○○ Very low

AE: Antiepileptics; MAD: Modified Atkins diet; NE: Not estimable; a: Lack of blinding; b: The study compares MAD with antiepileptics versus antiepileptics alone instead of MAD alone vs antiepileptics alone. However, it seems the only ethically feasible way to perform this comparison in a clinical trial; c: No events reported in the control group; d: Only one small study was included, *Relative effect: Not estimable due to a group without any event in the study period, **Absolute effect: Not estimable due to a group without any event in the study period.

monal therapy and vigabatrin.[27] Additionally, pyridoxine/pyridoxal phosphate, as monotherapy[28] or as an adjunct to first-line treatment,[29] and immunoglobulin monotherapy[30] have shown poor efficacy according to currently available evidence. Thus, they should be used only as a last resource for second-line treatment in patients with refractory West syndrome. Finally, Chandra et al. found a good response (more than 80% reduction of spasms) with valproate as first-line therapy in 39.5% of infants with West syndrome,[31] but there are no studies about the effect of valproate in RISS.

Regarding ketogenic dietary therapies, there have been several studies showing that this type of therapy achieves a seizure-free survival rate of 23-62% and a partial seizure control rate of 27-77% in children with RISS.[32]

However, we did not find RCTs comparing ketogenic diet (or a variant of this) without antiepileptics versus anticonvulsant medication alone, probably due to ethical and medical concerns related to the risk of even worsening spasm control in children who using this medication already have a poor control of their disease. Instead, the randomized controlled trial that was close to compare the efficacy of a dietary therapy versus antiepileptic medication was the one published by Sharma et al. in 2021.[20]

The trial by Sharma et al. compared the efficacy of MAD versus normal diet in children with RISS receiving anticonvulsant medication.[20] In the diet group, the efficacy rate of spasm cessation and ≥ 50% reduction was 23.9 and 65.2%, respectively.[20] In the control group, none of the children had a reduction in spam frequency.[20] Thus, it seems that coupling MAD with anticonvulsant treatment is superior to using only anticonvulsant medication in RISS. However, we found a high risk of bias. Spasm frequency reduction was assessed according to parental spasm records,[20] which is a potential source of bias in measurement of the outcome. As the authors of the study state, parental reports of spasms may not have been accurate, as nocturnal and subtle spasms are likely to be missed.[20] On the other hand, the lack of blinding in the study[20] is an important source of risk of bias due to potential non-adherence to a normal diet in the control group.

Epilepsy surgery has been shown to be effective in certain situations, for example, when there is a structural etiology,[1,33] reaching a complete seizure resolution rate as high as 79%.[34] However, there is no consensus on which is the best approach to select the best surgical candidates. One of the main problems is the lack of RCTs, as shown in a recent meta-analysis by Kolosky et al. looking for surgery outcomes and predictors of a favorable seizure outcome in children with epileptic spasms,[35] which is a wider population than the one we studied (we analyzed only studies in children with RISS). The study by Kolosky et al. found only retrospective studies.[35] The main limitation to perform RCTs comparing surgical treatment and other treatment modalities is the ethical issues arising from withholding a potential curative treatment (surgery) in severely affected children (lack of equipoise).[36] This has been highlighted after three RCTs comparing surgical and medical treatment in temporal lobe epilepsy patients published in 2000, 2012 and 2018, which were performed in circumstances that avoided – mostly – the problem of lack of equipoise.[36] New similar studies have not been published in epilepsy patients or in a specific subpopulation.

In conclusion, there is a lack of high-quality RCTs comparing treatment modalities (anticonvulsive medications, ketogenic diet or surgery) for patients with RISS. The need for further research is urgent given the devastating nature of this condition, and the burden it places on patients and caregivers.

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Ethical considerations: *Since this systematic review did not involve human subjects, either directly or indirectly, ethical approval was not obtained.*

Funding: *This research was self-funded.*

Conflicts of interest: *The authors declare that they have no conflicts of interest.*