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YEARBOOK

Under the Aegis of
Indian Academy of Neurology

Yearbook of NEUROLOGY 2022

Editors
Kalyan B Bhattacharyya
Gagandeep Singh

JAYPEE

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Section 4: Epilepsy

Section Editor: Viswanathan LG, Sinha S

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ARTICLE 1

Epilepsy Outcome at Four Years in a Randomized Clinical Trial Comparing Oral Prednisolone and Intramuscular ACTH in West Syndrome

Wanigasinghe J, Arambepola C, Ranganathan SS, Jayasundara K, Weerasinghe A, Wickramarachchi P. Epilepsy outcome at four years in a randomized clinical trial comparing oral prednisolone and intramuscular ACTH in West syndrome.

Pediatr Neurol. 2021;119:22-6.

Abstract

Objective: This study aimed to examine the role of oral steroids versus adrenocorticotropic hormone (ACTH) in controlling spasms in West syndrome.

Methods: The Sri Lanka Infantile Spasm Study is a prospective clinical trial aimed to evaluate the response to intramuscular ACTH compared with oral prednisolone. A previous study reported response through the age of 12 months. However, this study provides 4-year follow-up data.

Results: Of a total sample of 97 children, 13 had died, 19 could not be traced or contacted, and only 65 were available for follow-up at 4 years. Of the 65 children, 37 (57%) children continued to have seizures and 28 children were free of seizures. In the children with ongoing epilepsy, 32% continued to experience spasms, either alone or in combination with other types of seizures. Types of epilepsies observed in these children were focal epilepsy (59.4%), mixed focal and generalized epilepsy (24%), generalized epilepsy only (10.8%), and unknown (5%). Most of the children who were still having epilepsy (66.7%) were controlled with seizure medication. No significant difference was observed in the rate of epilepsy or spasms or control by medication between those treated with ACTH or oral prednisolone. Control of spasms at day 14 did not affect the 4-year spasm or epilepsy outcome.

Conclusion: Most of the children diagnosed with West syndrome continued to have seizures at the age of 4 years, though most were controlled with antiseizure medication. In addition, the long-term risk of developing epilepsy or its control was the same regardless of whether ACTH or prednisolone was used as initial treatment.

COMMENT

The ideal first-line treatment for infantile spasms is still up for debate. Hormonal treatments were found to have considerably better control of spasms on day 14 than vigabatrin in the United Kingdom Infantile Spasms Study (UKISS).[1] The authors have discussed the 4-year follow-up data of the Sri Lanka Infantile Spasm Study which was a prospective clinical trial that pitted intramuscular adrenocorticotropic hormone (ACTH) against oral prednisolone. They had observed there was no difference between the two with respect to control of seizures over 4 years. The spasm control at day 14 did not influence the epilepsy outcomes over the long term. Though there is reasonable evidence for administering steroids to reduce the frequency of seizures, long-term effects of steroid therapy on epileptic encephalopathy is largely unknown.[2] The International Collaborative Infantile Spasm Study involving 377 children, evaluated the effect of vigabatrin plus steroid treatment as a combination therapy for infantile spasms. Due to the possibility of vigabatrin-induced visual problems, the initial benefit of combination therapy becomes unclear in the absence of a clear long-term benefit.[3] Intuitively, one may hypothesize that its role in this regard is minimal as steroids do not modify the underlying disease process. It is rather more plausible that the cause of the epileptic encephalopathy may influence the long-term prognosis both epilepsy and development wise rather than steroid therapy.

ARTICLE 2

Safety and Tolerability of Transdermal Cannabidiol Gel in Children with Developmental and Epileptic Encephalopathies: A Nonrandomized Controlled Trial

Scheffer IE, Hulihan J, Messenheimer J, Ali S, Keenan N, Griesser J, et al. Safety and tolerability of transdermal cannabidiol gel in children with developmental and epileptic encephalopathies: A nonrandomized controlled trial.
JAMA Netw Open. 2021;4(9):e2123930.

Abstract

Objective: This study aimed to examine the tolerability and safety of cannabidiol (CBD) transdermal gel in children with developmental and epileptic encephalopathies (DEEs) and to evaluate its impact on seizure frequency, sleep, and quality of life.

Methods: This nonrandomized controlled trial was conducted at two centers in Australia and New Zealand from April, 2018 to July, 2019. Inclusion criteria involved children and adolescents aged 3–18 years with DEEs and were receiving a stable regimen of one to four antiseizure medications. Patients entered a flexible dosing maintenance period of 5.5 months, after 1-month baseline and

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titration periods, for a total 6.5 month treatment period. Data were analyzed throughout the 6.5 months of the treatment. CBD transdermal gel was applied twice daily at doses of 125–500 mg for 6.5 months.

Results: Safety and tolerability of the transdermal gel were assessed by reported adverse events (AEs) and skin examination. Median percent change from baseline to monthly (28-day) frequency of focal impaired awareness seizures (FIAS) and tonic-clonic seizures (TCS) over a period of 6.5 months was the primary outcome of this study.

Of 48 patients [mean age 10.5, standard deviation (SD) 3.8 years; number of boys: 26, 54%], 29 (60%) patients had at least one treatment-related AE over 6.5 months. Furthermore, 96% (44/46) of the treatment-related AEs were mild or moderate. Application-site dryness, application-site pain, and somnolence [each reported by 4 (8%) patients] were the reported treatment-related AEs in at least 5% of the patients. Diarrhea was reported as the only treatment-related gastrointestinal AE, which was reported in a single patient. Treatment with CBD gel was associated with reduction in the frequency of FIAS and TCS. Analysis of 33 patients with FIAS and TCS showed a median monthly reduction in seizures of 58% [interquartile range (IQR) −5.3% to 81.8%] at 5 months and 43.5% (IQR −23.8% to 57.5%) over the entire 6.5-month period. Improvements in social or interpersonal engagement and irritability (33/43, 77% participants); alertness, energy, and sleep (23/43, 53%); and cognition or concentration (20/43, 47%) were observed by the parents and caregivers.

Conclusion: In conclusion, CBD transdermal gel is a safe, well-tolerated treatment for children with DEEs, and is associated with reduction in frequency of FIAS and TCS and disease burden.

COMMENT

Cannabidiol (CBD) in epilepsy has generated a lot of research interest, especially in individuals with refractory and difficult to treat epilepsy.[4] This study aims to assess the safety and tolerability of transdermal CBD in children with developmental and epileptic encephalopathy (DEE). Children with DEE may have trouble taking medication orally and this can adversely impact drug adherence. Transdermal drug administration avoids first pass metabolism and effectively results in uniform drug levels in blood. This improves drug efficacy, reduces the dosage required, and avoids peak concentration-related side effects. Though this study was unblinded and did not have a control group, the authors observed transdermal application was safe. Not only did the seizure frequency reduce but caregivers also noticed some improvement in cognition and alertness. The absence of a control group makes it difficult to establish the effect size. Add-on CBD was proven to be effective in controlling seizures associated with Lennox–Gastaut syndrome (LGS) and Dravet syndrome (DS) in phase-3 clinical trials in recent times.[3,5,6] CBD as an adjuvant therapy to antiseizure medications (ASMs) and nonpharmacological treatments in children with drug-resistant epilepsy appears to be efficacious in reducing seizure duration and frequency, and may have a favorable impact on quality of life as reported by families.

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ARTICLE 3

Cost-effectiveness of Adrenocorticotropic Hormone versus Oral Steroids for Infantile Spasms

Sánchez Fernández I, Amengual-Gual M, Gaínza-Lein M, Barcia Aguilar C, Bergin AM, Yuskaitis CJ, et al. Cost-effectiveness of adrenocorticotropic hormone versus oral steroids for infantile spasms.
Epilepsia. 2021;62(2):347-57.

Abstract

Objective: In this study, the efficacy and cost-effectiveness of adrenocorticotropic hormone (ACTH) and oral steroids as first-line treatment for resolution of infantile spasms was explored.

Methods: A decision analysis model was populated with effectiveness data from a systematic review and meta-analysis of preexisting literature and cost data from publicly available prices. Effectiveness was defined as the probability of resolution of clinical spasms 14 days after initiation of treatment.

Results: In total, 21 studies with a total of 968 patients were included in the study. There was no statistically significant difference in the effectiveness of ACTH as compared with oral steroids [0.70, 95% confidence interval (CI) 0.60–0.79 vs. 0.63, 95% CI 0.56–0.70; $p = 0.28$]. Considering only three available randomized trials consisting of 185 patients, the odds ratio of resolution of spasms at 14 days with ACTH compared with high-dose prednisolone (4–8 mg/kg/day) was 0.92 (95% CI 0.34–2.52; $p = 0.87$). When adjusted for potential publication bias, the estimates became more favorable to high-dose prednisolone. In United States currency, high-dose prednisolone was a more cost-effective treatment, at an incremental cost-effectiveness ratio (ICER) of US $333 per case of spasms resolved, followed by ACTH, with an ICER of US $1,432,200 per case of spasms resolved. The results obtained were robust to multiple sensitivity analyses and different assumptions. Prednisolone at 4–8 mg/kg/day was found more cost-effective than ACTH under a wide range of assumptions.

Conclusion: Existing evidence does not support the superiority of ACTH in terms of efficacy and, especially, cost-effectiveness for resolution of infantile spasms 2 weeks after initiation of treatment.

COMMENT

Adrenocorticotropic hormone (ACTH) has been the mainstay of treatment for infantile spasms/West syndrome (WS). Available evidence has demonstrated that ACTH as well as steroids reduces infantile spasm frequency and also results in resolution of hypsarrhythmia when treatment is successful.[7] The purported advantage that ACTH has over steroids is its ability to also interact with ACTH receptors and interaction with these receptors may also alter epileptogenesis. However, clear evidence to support these claims is lacking. The high cost and lack of availability of ACTH are its inherent disadvantages.

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Varying doses of steroid therapy administered orally or parenterally (low to high) have also been shown to improve seizure outcomes in WS. In this study, oral steroids have had comparable efficacy as compared to ACTH. High-dose prednisolone had the lowest incremental cost-effectiveness ratio (ICER) at per case of spasms resolved. These findings held up to multiple sensitivity analyses and assumptions and prednisolone was definitely cost effect. Studies from India have supported the use of steroids in WS and other epileptic encephalopathies (EEs) and various steroid regimens have been used. Chatterjee et al. reported a large retrospective study documenting the successful use of intravenous pulse methylprednisolone (IVMP) in EE.[2] A randomized trial from Northern India comparing IVMP versus oral steroids observed the oral steroids arm did not observe any significant difference between these two modalities.[8] Due to the heterogeneity in the etiology and variable clinical course, prognostication using group statistics from such trials is difficult. It is possibly safe to say that steroids in some form are indicated in this patient age group; however, the dose, duration, and type of steroid to be used are still in contention and provide grounds for future trials.

ARTICLE 4

The SANTÉ Study at 10 Years of Follow-up: Effectiveness, Safety, and Sudden Unexpected Death in Epilepsy

Salanova V, Sperling MR, Gross RE, Irwin CP, Vollhaber JA, Giftakis JE, et al.; SANTÉ Study Group. The SANTÉ study at 10 years of follow-up: Effectiveness, safety, and sudden unexpected death in epilepsy.
Epilepsia. 2021;62(6):1306-17.

Abstract

Objective: This study aimed to evaluate the safety and efficacy of deep brain stimulation (DBS) of anterior nucleus of the thalamus after 7 and 10 years, and to report the incidence of sudden unexpected death in epilepsy (SUDEP) and overall mortality in adults in the Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy (SANTÉ) study.

Methods: After the blinded and unblinded phases of 3 months and 9 months, respectively, participants continued to be assessed during long-term follow-up (LTFU) and later a continued therapy access phase (CAP) to characterize adverse events and the incidence of SUDEP. Stimulus parameter and medication changes were allowed.

Results: A total of 110 implanted participants accumulated a total of 938 device-years of experience (69 subjects during the LTFU phase and 61 subjects in the CAP phase). Before study closure, 57 active participants continued therapy at 14 study centers, with follow-up of at least 10 (maximum 14) years. At 7 years, median percent reduction in seizure frequency from baseline was 75% ($p < 0.001$), with no outcome differences related to prior vagus nerve stimulation (VNS)

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or resective surgery. Focal to bilateral tonic-clonic, the most severe seizure type, was reported to be reduced by 71%. Adding new antiseizure medications did not affect the pattern of seizure reduction over time. Overall, there were no unanticipated serious adverse events in the study. The definite-plus-probable SUDEP rate, based on SANTÉ study experience (2 deaths in 938 years) and previous pilot studies (0 deaths in 76 years), indicated a rate of 2.0 deaths for 1,000 person-years. The overall mortality was 6.9 deaths per 1,000 person-years.

Conclusion: Overall, the findings report that the long-term efficacy and safety profiles of the DBS system for epilepsy are favorable and show stable outcomes. Improvement in frequency of the most severe seizure type may reduce risk of SUDEP. The rate of SUDEP with DBS (2.0) is comparable with other neuromodulation treatments (i.e., VNS and responsive neurostimulation) for drug-resistant focal epilepsy.

COMMENT

Refractory epilepsy that is not amenable for resective epilepsy surgeries can be truly challenging to treat. Neuromodulation has offered an alternative treatment option for such patients. The main contention for deep brain stimulation (DBS) as a successful antiepileptic therapy is the same as it is for movement disorders: within the target structure, possible cellular inhibition or excitement (neuromodulation).[9,10] As with any neuromodulatory technique [i.e., vagus nerve stimulation (VNS)/DBS, etc.], it is now known that with time, outcomes improve. This 10-year follow-up of the Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy (SANTÉ) trial has reposed faith in that notion with 75% reduction in seizure frequency noted after 7 years of implantation. 7-year retention was 66%, with discontinuations due to lack of benefit (24%), death (6%), and implant site infection. (5%). The mean response rate was 74%, with 8% of patients were seizure free for 2 years or more. Last observation carried forward and other sensitivity methods were used to analyze the impact of missing data. Controlling for patient attrition, new autism spectrum disorders (ASDs), past VNS therapy, or epileptogenic zone location had no impact on the results. Notably, patients with uni- or bitemporal lobe seizures had higher effectiveness. Concerningly, mental disorders, which are prevalent comorbidities in drug-resistant epilepsy, may limit utilization of this therapy. Depression was noted in 37.3% of participants, 67% of whom had a history of depression and suicidality in 10%. Memory impairment was noted in 30% of subjects, 50% of whom already had memory issues, although no comprehensive neuropsychological test was conducted. These adverse events (AEs) were highly prevalent yet resulted in few discontinuations. The long-term follow-up (LTFU) data from the SANTÉ trial[11] is encouraging; however, there are many more questions—the optimal stimulation parameters, choosing the appropriate site, and if there is a difference in outcome between DBS versus other neuromodulatory techniques.

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ARTICLE 5

Identifying Seizure Risk Factors: A Comparison of Sleep, Weather, and Temporal Features using a Bayesian Forecast

Payne DE, Dell KL, Karoly PJ, Kremen V, Gerla V, Kuhlmann L, et al. Identifying seizure risk factors: A comparison of sleep, weather, and temporal features using a Bayesian forecast.
Epilepsia. 2021;62(2):371-82.

Abstract

Objective: Most of the algorithms that forecast seizures rely on features that are specific to recordings of an electroencephalogram (EEG). Various environmental and physiological factors, such as weather and sleep, have been claimed to influence brain activity and occurrence of seizures but have not been fully investigated as prior information for forecasting seizures in a patient-specific analysis. This study aimed to quantify whether sleep, weather, and temporal factors (time of day, day of week, and lunar phase) can provide predictive prior probabilities that may be used to advance the forecasting of seizures.

Methods: This study performed a post-hoc analysis on data from eight patients with a total of 12.2 years of continuous intracranial electroencephalographic recordings (average = 1.5 years, range = 1.0–2.1 years) that were collected in a prospective trial. In addition, patients had sleep scoring and location-specific weather data. Histograms of future seizure likelihood were generated for each feature. A Bayesian approach was used to combine different factors into an overall forecast of seizure likelihood for measuring the predictive utility of individual factors. Area under the receiver operating curve was used to compare the performance of different feature combinations. However, performance evaluation was pseudoprospective.

Results: For the eight patients who were included in the study, seizures could be predicted above chance accuracy using sleep (five patients), weather (two patients), and temporal features (six patients). Forecasts using combined features performed significantly better than chance in six patients. For four of these patients, combined forecasts outperformed any individual feature.

Conclusion: To conclude, data with regard to environmental and physiological factors, including sleep, weather, and temporal features, provide significant predictive information on seizures forecasts. Although both the forecasts and the algorithms that use invasive intracranial electroencephalography did not perform, the results were significantly above chance. Furthermore, complementary signal features derived from an individual's previous seizure records may provide useful information to boost the detection of traditional seizures or augment the forecasting algorithms. Most importantly, many predictive features used in this study can be measured noninvasively.

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COMMENT

Meteorological events have long been assumed to affect health, but reliable scientific proof is lacking. Accurate prediction models that can reliably forecast seizure recurrence is also inadequate. Most algorithms deal with data obtained from patient-centric data. There is a growing body of evidence that indicts environmental factors in the occurrence of seizures.[12-14] This study is a post-hoc analysis that attempts to describe a seizure model with intracranial electroencephalogram (EEG), sleep, and environmental data. The authors investigated sleep, temporal variables (clock and calendar time), and weather as seizure predictors. In order to examine seizure forecasting for different feature categories, continuous long-term EEG recordings were used. Though intracranial EEG data improved performance of the algorithms, forecasting was possible to a certain extent using noninvasive data and historical seizure records from seizure diaries. Of all the studied variables, time of the day was most significant in forecasting seizures and weather indicators did not perform well. The results from this study provide complementary features that can be used in conjunction with or in lieu of invasively measured features. Better understanding patient-specific risk variables may lead to clinical seizure forecasting for epilepsy patients in the future using deep-learning/artificial intelligence (AI)-enabled applications.

ARTICLE 6

The SANAD II Study of the Effectiveness and Cost-effectiveness of Valproate versus Levetiracetam for Newly Diagnosed Generalized and Unclassifiable Epilepsy: An Open-label, Non-inferiority, Multicenter, Phase 4, Randomized Controlled Trial

Marson A, Burnside G, Appleton R, Smith D, Leach JP, Sills G, et al.; SANAD II collaborators. The SANAD II study of the effectiveness and cost-effectiveness of valproate versus levetiracetam for newly diagnosed generalised and unclassifiable epilepsy: An open-label, non-inferiority, multicentre, phase 4, randomised controlled trial.
Lancet. 2021;397(10282):1375-86.

Abstract

Objective: This study aimed to compare the long-term efficacy and cost-effectiveness of levetiracetam (LEV) compared with valproate in patients with a newly diagnosed generalized epilepsy or unclassified epilepsy. Valproate is a first-line treatment for patients with newly diagnosed idiopathic generalized or unclassified epilepsy. However, it is not advisable for women of childbearing potential because of its teratogenicity. LEV is increasingly prescribed for these patient populations despite paucity of evidence about its clinical efficacy or cost-effectiveness.

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Methods: This study is an open-label, randomized controlled trial (RCT) to compare LEV with valproate as a first-line treatment for patients with generalized or unclassified epilepsy. Adult and pediatric neurology services (69 centers overall) across the United Kingdom recruited participants who were aged ≥5 years (with no upper age limit) and reported ≥2 unprovoked generalized or unclassifiable seizures. Participants were randomly allocated in a 1:1 ratio to receive either LEV or valproate, using a minimization program with a random element utilizing factor. The treatment allocation was known to the participants and investigators. Initial advisable maintenance doses were 500 mg twice a day for LEV and valproate for participants who were aged ≥12 years and 25 mg/kg for valproate and 40 mg/kg for LEV for participants aged 5–12 years. Both drugs were administered orally. SANAD-II was designed to compare the noninferiority of LEV with valproate for the primary outcome time to 12-month remission. The noninferiority limit was a hazard ratio (HR) of 1.314, which equates to an absolute difference of 10%. A HR >1 indicated that an event was more likely on valproate. All participants were included in the intention-to-treat (ITT) analysis. Per-protocol (PP) analyses excluded participants with major protocol deviations and those who were subsequently diagnosed as not having epilepsy. All participants who received one dose of any of the drug under study were included in the safety analyses.

Results: A total of 520 participants were recruited for the study between April 30, 2013, and August 2, 2016, and were followed up for a period of 2 years. Of these, 260 (50%) participants were randomly allocated to receive LEV and 260 (50%) participants were allocated to receive valproate. The ITT analysis included all participants and the PP analysis included 255 participants randomly allocated to valproate and 254 randomly allocated to LEV. Median age of participants was 13.9 years (range 5.0–94.4). Overall, 65% of the participants were male and 35% of the participants were female. Of 520 participants, 397 reported to have generalized epilepsy, whereas 123 had unclassified epilepsy. LEV did not meet the criteria for noninferiority in the ITT analysis of time to 12-month remission [HR 1.19 (95% CI 0.96–1.47); noninferiority margin 1.314]. The PP analysis showed that the 12-month remission was superior with valproate than with LEV. There were two deaths, one in each group, which were unrelated to trial treatments. Adverse reactions were reported by 96 (37%) participants randomly assigned to valproate and 107 (42%) participants randomly assigned to LEV. LEV was dominated by valproate in the cost-utility analysis, with a negative incremental net health benefit of −0.040 (95% central range −0.175 to 0.037) and a probability of 0.17 of being cost-effective at a threshold of £20 000 per quality-adjusted life year. Cost-effectiveness was based on differences between treatment groups in costs and quality-adjusted life year.

Conclusion: It was found that LEV was neither clinically effective nor cost-effective as compared with valproate. Furthermore, these results inform the discussions pertaining to benefit and harm of avoiding valproate in girls and women of childbearing potential.

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COMMENT

With the advent of newer antiseizure medications, the burgeoning question has been are they better than the older drugs? Surprisingly, the results of SANAD-II did not lend much support to the use of levetiracetam (LEV) in generalized and unclassifiable epilepsy. In light of its favorable adverse effect profile, few drug interactions and reasonable efficacy in many seizure types; LEV has gained popularity since its introduction in 1999. Morso, it was proven to be safe for women in childbearing, pregnancy, and lactation.[15] On the other hand, LEV is associated with an increased risk of reversible neuropsychiatric adverse effects that may occur in up to 10–13% of adults. In this randomized controlled trial (RCT), LEV was shown to be inferior to valproic acid (VPA) in the time to achieve long-term (1 and 2 year) seizure remission (12-month seizure freedom: LEV: 24%; VPA: 33%). Surprisingly, there was no difference in treatment failure due to side effects. These findings lead the authors to recommend VPA as the first-line medication in generalized epilepsy. However, women in the childbearing age group will remain an exception to this recommendation. A prior randomized trial[16] and a meta-analysis[17] had reported that LEV was inferior to sodium channel blockers (carbamazepine and lamotrigine) in focal epilepsy and to VPA in generalized epilepsy. The "user-friendliness" of LEV has probably precluded the thorough consideration of its efficacy when starting first-line management for many including non-neurologists. If we are to go by the SANAD-II results, LEV may not be the obvious effective choice in the long term.

ARTICLE 7

Prevention of Epilepsy in Infants with Tuberous Sclerosis Complex in the EPISTOP Trial

Kotulska K, Kwiatkowski DJ, Curatolo P, Weschke B, Riney K, Jansen F, et al. EPISTOP Investigators. Prevention of epilepsy in infants with tuberous sclerosis complex in the EPISTOP trial.
Ann Neurol. 2021;89(2):304-14.

Abstract

Objective: Epilepsy develops in 70–90% of children with tuberous sclerosis complex (TSC) and is often resistant to treatment medications. However, recently, the concept of preventive antiepileptic treatment to alter the natural history of epilepsy has been proposed. EPISTOP was a clinical trial designed to compare preventive with conventional antiepileptic treatment in infants with TSC.

Methods: In this multicenter study, 94 infants with TSC without any history of seizures were followed with monthly video electroencephalography (EEG). The infants received vigabatrin

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either as a conventional antiepileptic treatment, started after the first electrographic or clinical seizure, or preventively when an epileptiform EEG activity was detected before seizures. At 6 sites, participants were randomly allocated to treatment in a 1:1 ratio in a randomized controlled trial (RCT). At 4 sites, treatment allocation was fixed; this was denoted an open-label trial (OLT). Participants were followed up to 2 years of age. Time to first clinical seizure was defined as the primary endpoint.

Results: Epileptiform EEG abnormalities were identified before seizures in 54 participants. Of these, 27 participants were included in the RCT and 27 participants were included in the OLT. The time to the first clinical seizure was significantly longer with preventive than conventional treatment [RCT 364 days (95% confidence interval (CI) 223–535] vs. 124 days (95% CI 33–149); OLT 426 days (95% CI 258–628) vs. 106 days (95% CI 11–149)]. At 24 months, our pooled analysis showed that the preventive treatment reduced the risk of clinical seizures [odds ratio (OR) 0.21; $p = 0.032$), drug-resistant epilepsy (OR 0.23; $p = 0.022$), and infantile spasms (OR 0; $p < 0.001$). No adverse events related to preventive treatment were observed.

Conclusion: This study concluded that the preventive treatment with vigabatrin was safe, modified the natural history of seizures in TSC, thereby reducing the risk and severity of epilepsy.

COMMENT

The "holy grail" of epilepsy treatment is to stop the process of epileptogenesis. A majority of patients with tuberous sclerosis complex (TSC) suffer from epilepsy and is usually refractory to conventional treatment. A growing body of evidence has supported the notion that the natural history of epilepsy could be modified with medical treatment. Vigabatrin is the first line medication for TSC-associated spasms or seizures in the first year of life. Also, vigabatrin appears to block mammalian target of rapamycin (mTOR) activation in animal experiments, suggesting a dual involvement in epileptogenesis.[18] Vigabatrin may be used presymptomatically or in the presence of epileptiform abnormalities on electroencephalography (EEG). In this case, epileptiform discharges on EEG were 100% predictive of epilepsy onset in a group of 40 TSC patients.[19] In the EPISTOP trial, vigabatrin was given to subset of children with TSC who also had EEG abnormalities before the first episode of seizure. This group was compared with patients who received treatment after the first episode. After 24 months, it was observed that preventive treatment significantly reduced the odds of developing clinical seizures, drug resistant epilepsy, and spasms. In fact, none of the children who received preventive therapy suffered from infantile spasms. Secondary outcomes for neurodevelopmental measures were not met. There were no adverse events related to preventive treatment. In TSC, early onset of epilepsy is a predictor of poor neurodevelopmental outcomes.[20] EPISTOP study has remarkably demonstrated that a simple intervention may alter the natural history of epilepsy in TSC, however, number of patients were small and real-world experience of preventive therapy in TSC may throw more light on its efficacy.

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ARTICLE 8

When Should a Brain MRI be Performed in Children with New-onset Seizures? Results of a Large Prospective Trial

Hourani R, Nasreddine W, Dirani M, Hmaimess G, Sabbagh S, El Tourjuman O, et al. When should a brain MRI be performed in children with new-onset seizures? Results of a large prospective trial.
AJNR Am J Neuroradiol. 2021;42(9):1695-701.

Abstract

Objective: There is a scarcity of data with regard to the incidence of structural brain lesions in children with new onset unprovoked seizures. This study aimed to determine the frequencies and types of epileptogenic lesions detected on a dedicated epilepsy protocol magnetic resonance (MR) imaging according to age group, presence of developmental delay, and number and types of seizures.

Methods: This study included children between the age group of 6 months and 18 years and with new-onset unprovoked seizures. The frequencies and types of epileptogenic lesions were determined and then stratified according to sex, age groups, presence of developmental delay, and number and types of seizures at presentation. Multivariate analysis was used to identify variables significantly associated with the presence of epileptogenic lesions.

Results: A total of 1,000 children were included in the study. An epileptogenic lesion was identified in 26% of the children. Malformations of cortical development were the most common lesion (32%), followed by hypoxic-ischemic injury (20%), and vascular etiologies (16%). Univariate analysis showed a significant increase in the frequency of epileptogenic lesions with a decrease in age, presence of developmental delay, and number and types of seizures at presentation. Presence of developmental delay and type of seizures at presentation remained significant in a multivariate analysis.

Conclusion: This study reported a relatively high rate of epileptogenic lesions in children with new-onset seizures. Furthermore, presence of developmental delay and specific seizure types were associated with a higher likelihood of detecting an epileptogenic lesion on neuroimaging. This study meets the requirements of the study design as per the recommendations of the Practice Committee of the American Academy of Neurology. The authors hope that these results will help the relevant societies and committees in drafting guidelines for neuroimaging for children with new-onset seizures.

COMMENT

In resource-limited settings, imaging modalities may not be easily accessible or affordable. According to the International League Against Epilepsy (ILAE) Subcommittee for Pediatric Neuroimaging, over half of children with new-onset focal seizures have abnormal neuroimaging, which offers information on etiology and localization.[21] This study by

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