Corticosteroids versus clobazam for treatment of children with epileptic encephalopathy with spike-wave activation in sleep: a multicentre randomised controlled trial (RESCUE ESES)

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Summary
Background Epileptic encephalopathy with spike-wave activation in sleep (EE-SWAS) is a rare disorder associated with cognitive and behavioural regression. On the basis of mostly small observational and retrospective studies, corticosteroids and clobazam are often considered the most effective treatments for this syndrome. We aimed to compare cognitive outcomes of children with EE-SWAS 6 months after starting treatment with either corticosteroids or clobazam.
Methods We did a multicentre, randomised controlled trial at eight tertiary referral centres for rare epilepsies in seven European countries. Children were eligible to participate if they were aged 2–12 years, were diagnosed with EE-SWAS within 6 months before inclusion, and had not been treated with corticosteroids or clobazam previously. Participants were randomly assigned (1:1) to treatment with corticosteroids (either continuous treatment with 1–2 mg/kg per day of prednisolone orally or

pulse treatment with 20 mg/kg per day of methylprednisolone intravenously for 3 days every 4 weeks) or clobazam (0·5–1·2 mg/kg per day orally). The primary outcome was cognitive functioning after 6 months of treatment, which was assessed by either the intelligence quotient (IQ) responder rate (defined as improvement of ≥11·25 IQ points) or the cognitive sum score responder rate (defined as improvement of ≥0·75 points). Safety was assessed by number of adverse events and serious adverse events. Data were analysed in the intention-to-treat population, which included all children as randomised who had primary outcome data available at 6 months. The trial is registered with the Dutch Trial Register, Toetsingonline, NL43510.041.13, and the ISRCTN registry, ISRCTN42686094. The trial was terminated prematurely because enrolment of the predefined number of 130 participants was deemed not feasible.

Findings Between July 22, 2014, and Sept 3, 2022, 45 children were randomly assigned to either corticosteroids (n=22) or clobazam (n=23); two children assigned clobazam dropped out before 6 months and were excluded from the intention-to-treat analysis. At the 6-month assessment, an improvement of 11·25 IQ points or greater was reported for five (25%) of 20 children assigned corticosteroids versus zero (0%) of 18 assigned clobazam (risk ratio [RR] 10·0, 95% CI 1·2–1310·4; p=0·025). An improvement of 0·75 points or more in the cognitive sum score was recorded for one (5%) of 22 children assigned corticosteroids versus one (5%) of 21 children assigned clobazam (RR 1·0, 95% CI 0·1–11·7, p=0·97). Adverse events occurred in ten (45%) of 22 children who received corticosteroids, most frequently weight gain, and in 11 (52%) of 21 children who received clobazam, most often fatigue and behavioural disturbances. Occurrence of adverse events did not differ between groups (RR 0·8, 95% CI 0·4–1·4; p=0·65). Serious adverse events occurred in one child in the corticosteroid group (hospitalisation due to laryngitis) and in two children in the clobazam group (hospitalisation due to seizure aggravation, and respiratory tract infection). No deaths were reported.

Interpretation The trial was terminated prematurely and the target sample size was not met, so our findings must be interpreted with caution. Our data indicated an improvement in IQ outcomes with corticosteroids compared with clobazam, but no difference was seen in cognitive sum score. Our findings strengthen those from previous uncontrolled studies that support the early use of corticosteroids for children with EE-SWAS.

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Research in context

Evidence before this study

We searched PubMed between database inception and April 30, 2023, with the search terms “clobazam” OR “benzodiazepines”, “corticosteroids” OR “steroids”, and “EE-SWAS” OR “ESES” OR “CSWS”, for randomised controlled trials, other clinical trials, reviews, systematic reviews, and meta-analyses published in English that assessed treatment effectiveness by cognitive or subjective cognitive improvement. We identified four non-systematic reviews and a meta-analysis from 2015 that we conducted. One non-systematic review suggested that benzodiazepines and sodium valproate are the most effective treatments for epileptic encephalopathy with spike-wave activation in sleep (EE-SWAS). A second non-systematic review reported low efficacy of most antiseizure medications in EE-SWAS and suggested high-dose benzodiazepines or corticosteroids. A third non-systematic review reported that an evidence-based management approach is scarce and that standard antiseizure medications, corticosteroids, and benzodiazepines can all be considered as first choices. The fourth non-systematic review reported a treatment effect for both corticosteroids and benzodiazepines and suggested steroid therapy as first-line treatment for EE-SWAS with a structural or metabolic cause. Benzodiazepines, valproate, or levetiracetam were considered first-line therapy for EE-SWAS with an unknown cause. Steroids were suggested when the proposed first-line treatment proved ineffective 6 months after initiation. Our 2015 meta-analysis included 112 studies and analyses of 950 individual treatments in 575 children with EE-SWAS. Subjective cognitive

improvement was reported in 45% of children treated with benzodiazepines and in 70% of those treated with steroids.

Added value of this study

This study is the first randomised controlled trial comparing corticosteroids with clobazam as initial treatment for EE-SWAS. Although uncontrolled observational studies have suggested superiority of corticosteroids over clobazam, the quality of the evidence is poor, particularly because subjective outcome measures were often used in the studies, treatment duration was highly variable, and adverse effects of treatment were frequently not accounted for in analyses. In practice, treatment choice in children with EE-SWAS has been mostly based on institutional preference and expert opinion. This trial was urgently needed to determine which of the prevailing treatment choices—corticosteroids or clobazam—is most effective and better tolerated.

Implications of all the available evidence

The results from this European, multicentre, randomised, controlled trial complement previous evidence from retrospective studies and indicate that, for early therapy, corticosteroids are superior to clobazam in improving cognitive function in children with EE-SWAS. This trial also shows that corticosteroids and clobazam are equally well tolerated in children with EE-SWAS.

Introduction

Epileptic encephalopathy with spike-wave activation in sleep (EE-SWAS) is a rare childhood epilepsy syndrome that accounts for less than 1% of epilepsy presentations seen at tertiary paediatric epilepsy centres.[1] The syndrome is characterised by onset of seizures between the ages of 2 and 12 years (mostly focal seizures, although other seizure types might occur, and in some cases, no clinical seizures are recorded), and by the presence of nearly continuous spike-wave discharges on EEG during sleep, accompanied by acquired cognitive deterioration and behavioural problems.[2] The typical EEG pattern consists of continuous spike-wave discharges during more than 85% of slow-wave sleep, previously labelled as electrical status epilepticus in sleep (ESES).[2,3] However, atypical cases with spike-wave discharges for 50–85% of the time asleep, and cases with significant developmental delay but without arrest or regression of development, are recognised and accepted by the International League Against Epilepsy (ILAE); thus, the syndrome was recently renamed EE-SWAS.[4,5]

The seizures and the EEG pattern of EE-SWAS usually resolve spontaneously around puberty. However, cognitive outcome is often disappointing, with permanent cognitive deficits in most children.[6] Several genetic and structural aetiologies—eg, *GRIN2A* mutations, polymicrogyria, and thalamic injuries—have been associated with EE-SWAS.[7,8] However, the cause of the syndrome remains unclear in many children.

For children with EE-SWAS, the goal of treatment is to prevent or minimise cognitive regression. It is unknown whether the spike-wave activation in sleep needs to be completely suppressed to improve cognitive function. A positive response to conventional antiseizure medications, including ethosuximide, levetiracetam, sulthiame, and valproic acid, has been described in some studies,[9,10] but their effect on cognition is usually disappointing.[11] Many small observational studies have reported that benzodiazepines and immunomodulating agents are the most effective treatment for children with EE-SWAS.[12–14] Although some of these studies have suggested superiority of corticosteroids over clobazam, solid evidence from controlled trials is scarce. Moreover, the adverse effects of treatment were often not accounted for in these studies.

In the RESCUE ESES trial, we aimed to investigate whether corticosteroids or clobazam are more effective as initial treatment for children with EE-SWAS, and which of these treatments is better tolerated.

Methods

Study design and participants

RESCUE ESES was a multicentre, randomised controlled trial with blinded outcome assessment, involving eight tertiary referral centres for rare epilepsies from seven European countries (Denmark, Finland, France, Germany, the Netherlands, Spain, and the UK). The study complies with the principles of the Declaration of Helsinki[15] and with applicable government regulations and institutional research policies and procedures. The study protocol and amendments were reviewed and approved by independent ethics committees or institutional review boards in agreement with local requirements. All parents or legal representatives of children provided written informed consent before enrolment. The trial protocol has been published in detail.[16]

Participants were candidates for inclusion if they were aged 2–12 years and were diagnosed with EE-SWAS within 6 months before inclusion. Both typical and atypical cases were eligible for this study. We defined typical EE-SWAS as bilateral sleep-aggravated epileptiform activity with a spike-wave index (SWI) of more than 85% in non-rapid eye movement (NREM) sleep on EEG, and developmental delay, arrest, or regression. We defined atypical EE-SWAS as either: (1) bilateral sleep-aggravated epileptiform activity with an SWI of more than 50% in NREM sleep on EEG and arrest or regression of development; (2) unilateral sleep-aggravated epileptiform activity with an SWI of more than 85% in NREM sleep on EEG, and arrest or regression of development; or (3) unilateral epileptiform activity with an SWI of more than 50% in NREM sleep on EEG and regression of development. A typical or atypical EE-SWAS diagnosis was made **based on** whole-night EEG recording.

Exclusion criteria were previous treatment with corticosteroids or clobazam, an SWI during wakefulness of more than 50%, an acute or chronic infectious disease (eg, tuberculosis or HIV infection) or any other condition that, according to the investigator, contraindicated the use of corticosteroids or clobazam. An additional exclusion criterion was current treatment with carbamazepine, oxcarbazepine, vigabatrin, tiagabine, gabapentin, and pregabalin, which might increase SWI and worsen outcome in children with EE-SWAS.[17]

Randomisation and masking

A data manager, independent of the study group, generated an online randomisation scheme with random permuted blocks (block sizes of one and two), and this scheme was uploaded into a secure online database (Research Online version 2; https://www.researchonline.org) to ensure concealment of treatment allocation. Block randomisation was stratified for centre to ensure equal allocation to each treatment group. Participants were randomly assigned (1:1) to treatment with corticosteroids or clobazam. Participants and treating physicians were not masked to the treatment assignment, because of the inherent differences in mode of administration and expected adverse effects between treatment groups. The neuropsychologists and neurophysiologist (EEG readers) who evaluated the outcome were masked to treatment assignment.

Procedures

For participants allocated to corticosteroids, either intravenous pulse methylprednisolone or continuous oral prednisolone was given, according to local experience and the preference of each study centre. In the case of pulse methylprednisolone, the dose was 20 mg/kg given over 30 min once daily for 3 consecutive days then at 4-week intervals for 6 months. In the case of oral prednisolone, the dose was initially 2 mg/kg per day, to a maximum of 60 mg per day, for 1 month followed by 1–2 mg/kg per day (maximum 60 mg per day) for the next 5 months (dose decided by the treating physician).

For participants allocated to clobazam, the oral dose was titrated to 0·5 mg/kg per day within 2 weeks. If well tolerated, the dose was increased to a maximum of 1·2 mg/kg, once daily. If the

clobazam dose exceeded 20 mg per day, it could be divided in two daily oral administrations. Treatment was continued for at least 6 months,
In both treatment arms, if the child developed intolerable adverse effects or further cognitive regression, addition of or replacement with an alternative intervention, including switching to the other arm, could be applied as required in the treating physician's opinion. After 6 months, treatment could either be continued or the dose tapered according to the treating physician's preference. Alternative treatment options, thereafter, were allowed.

Before starting treatment, baseline characteristics were obtained, including type and occurrence of seizures in the previous 12 months, and the results of ancillary diagnostic investigations were recorded in an online data capture system. The whole-night EEG recording that was required for EE-SWAS diagnosis was considered the baseline EEG. A baseline neuropsychological assessment was also done before starting treatment. Follow-up visits were scheduled at 1, 3, 6, and 18 months after initiation of treatment. They included assessment of clinical status, seizure occurrence since the previous visit (recorded by parents or caregivers), any adverse effects, and an estimate of global daily functioning by parents or caregivers using a visual analogue scale (VAS). VAS scores assessed after treatment initiation ranged from –5 to 5, with scores above zero indicating improvement of global daily functioning compared with the last visit, and scores below zero indicating worsening of global daily function compared with the last visit. In the corticosteroid group, blood pressure, testing for protein and glucose in urine, and any need for stress prednisolone dosing were recorded at each follow-up visit as additional safety assessments. An EEG was done at every follow-up visit. A neuropsychological assessment was only done after 6 and 18 months of treatment to prevent test–retest bias.

For follow-up assessments, either a sleep-deprived EEG of at least 1 h or a whole-night EEG recording was considered adequate. At each EEG, spike-wave activity was analysed in a selected epoch of 10 min in the first NREM cycle, 5 min after alpha attenuation. The seconds with spike wave activity, in this whole epoch, were visually counted and divided by the total time (60 times 10 s) to calculate the SWI. In addition, the background pattern, presence, or absence of physiological sleep phenomena (ie, sleep spindles, K-complexes, and vertex waves) and localisation of epileptiform abnormalities were assessed.

Neuropsychological assessments were done by neuropsychologists who were masked to treatment. Depending on the age and abilities of each participant, tests were selected from a fixed battery covering six major domains of cognition (ie, intelligence, language, memory, attention, visuospatial functions, and executive functions). Reporting and scoring were done according to the test manuals. Individual raw test scores at baseline and follow-up were transformed into Z scores, on the basis of the mean and SD of standard scores. For each cognitive domain, a mean Z score was calculated. A cognitive sum score was then calculated to measure overall cognitive functioning, representing the mean Z score over the cognitive domains that were assessed. Intelligence quotient (IQ) or mental developmental index (MDI) were determined, depending on the type of tests children were able to undergo, considering their age and abilities. IQ was determined using either the Wechsler Intelligence Scale for Children (WISC-IV) or the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-IV). MDI was determined by the Bayley Scales of Infant Development. In specific cases, a non-verbal total score could be determined using the Wechsler non-verbal test. For participants receiving intravenous corticosteroids, neuropsychological assessments were done at least 14 days after the last intravenous methylprednisolone administration, to minimise any potential bias in test scores resulting from the potential alerting effect of corticosteroids.

Outcomes

The coprimary efficacy endpoints were two measures of cognitive function after 6 months of treatment. The first measure of cognitive function was the IQ responder rate, which we defined as the percentage of participants achieving an improvement of 11·25 IQ points or more (ie, 75% of the SD). We considered IQ, MDI, and non-verbal total score as valid measurements for total IQ, because these scores are derived from standardised tests that are designed to assess intelligence. These tests have the same normal distribution, with a mean of 100 and an SD of 15. In children with severe developmental delay (ie, MDI or IQ scores <55), mental development could not be identified more accurately than below the lowest mental developmental index provided in the manual. These cases were excluded from the IQ responder rate analysis. When no total IQ could be obtained (because of severe language deficits), performance IQ (if obtained) was considered a valid measurement for (non-verbal) total IQ. The second measure of cognitive function was the cognitive sum score responder rate, which we defined as the percentage of participants achieving an improvement of 0·75 points or more (ie, 75% of the SD). The cognitive sum score is a mean Z score (Z scores have a mean of 0 and an SD of 1) based on the Z scores of all (if obtained) cognitive domains (intelligence, language, memory, attention, visuospatial functions, and executive functions) that were assessed in each participant.

We assessed seven predefined secondary efficacy outcomes: (1) IQ responder rate at 18 months; (2) cognitive sum score responder rate at 18 months; (3) the change in IQ from baseline to 6 months and 18 months (delta IQ); (4) the change in cognitive sum score from baseline to 6 months and 18 months (delta cognitive sum score); (5) the change in SWI from baseline to 6 months and 18 months (delta SWI); (6) the proportion of participants who were EEG responders (defined as a decrease in SWI of ≥25% compared with baseline) at 6 months and 18 months; and (7) the change in global daily functioning (assessed using VAS scores) from baseline to 6 months and 18 months. Secondary safety outcomes were adverse events and serious adverse events, which were analysed descriptively.

We did a post-hoc analysis of the proportion of participants with seizures at 6 and 18 months, instead of our predefined secondary outcome measure of seizure frequency, because the clinical information collected in the electronic case report forms was insufficient to assess the frequency of seizures. We also assessed in a post-hoc analysis the proportion of participants with SWI during sleep of less than 50% on EEG at 6 months and 18 months. This analysis was done because it compares the proportion of participants who no longer meet the previous EEG criteria for ESES (SWI **≥**50%)

As part of the RESCUE ESES trial, we obtained serum samples to assess proinflammatory cytokine levels at baseline and 8 months after initiation of treatment. These results will be reported separately.

Statistical analysis

Due to no previous controlled trials, we based our sample size calculation on our meta-analysis of treatment effect in published cases with EE-SWAS, in which cognitive improvement was reported in 45% of participants treated with benzodiazepines and in 70% of those treated with corticosteroids.[11] We estimated that a sample size of 130 children (65 per treatment group) would provide 80% power to detect a 25% difference in responder rate (ie, the percentage of participants achieving improvement of ≥11·25 IQ points [75% of SD]) between the treatment groups, at a two-sided significance level of 0·05, accounting for a possible 10% drop-out rate.

We present baseline characteristics as absolute and relative frequencies for categorical data and mean (SD) or median (IQR) for continuous data. The primary and secondary outcomes were analysed according to the intention-to-treat principle (ie, participants with data for the primary outcome were

assessed according to the treatment to which they were randomised). Patients who had no data available for an outcome assessment were excluded from the analysis of that outcome.

Firth-type logistic regression was used to model differences in responder rates between treatment groups. This method was not prespecified in the protocol, but it was considered to provide the most appropriate approach to reduce the bias of the maximum likelihood estimates in the presence of separation.[18] Differences between treatment groups were presented as risk ratios (RRs) with 95% CIs.

We additionally did sensitivity analyses on our coprimary outcomes, which were not prespecified in our study protocol (appendix pp 4–5 Because the frequentist analysis relies on asymptotic normality, and our data are from a small number of participants, we did a complementary Bayesian analysis, obviating the need to adjust for degrees of freedom or to correct for finite sample sizes (appendix p 4 [19] We also report the proportion of participants who continued the treatment they were assigned to, those who switched to the other group, and those who combined the treatments of both groups after 6 months and 18 months (figure 1)

Categorical secondary outcomes were analysed by logistic regression, with differences presented as RRs with 95% CIs. Linear regression analysis was used to analyse continuous secondary outcomes when the underlying assumptions were met, with differences presented as regression coefficients (β) with 95% CIs. When these assumptions were violated, we used the non-parametric Wilcoxon sum test with continuity correction, with differences presented as median with IQR (appendix p 3).

Additional prespecified analyses were done to identify potential prognostic factors for treatment response. These possible predictors were prespecified in the study protocol based on previous literature and included age at first SWAS recording, the time interval between first SWAS recording and inclusion, IQ level and cognitive sum scores at inclusion, number of antiseizure medications administered before inclusion, and cause of EE-SWAS (unknown *vs* established structural or genetic cause). Multivariable linear regression was done to assess a relationship between the potential prognostic factors and delta IQ and delta cognitive sum score, because there were not enough IQ responders and cognitive sum score responders in the total group of participants for the prespecified multivariable logistic regression (according to protocol)(appendix p 6) . We considered p values less than 0·05 significant for all analyses.

For anonymised data collection, management, and storage, we used the clinical trial software Research Online version 2 . Analyses were done with the statistical software RStudio, version 1.3.1093. Data monitoring in the coordinating centre was done twice a year by an independent clinical research associate (Brain Centre, University Medical Center Utrecht, Utrecht, Netherlands; and Julius Clinical, Zeist, Netherlands) and in participating centres after first inclusion, once a year thereafter, and at close-out, by clinical trial units associated with the European Clinical Research Infrastructure Network.

This trial is registered with the Dutch Trial Register, ToetsingOnline, NL43510.041.13, and the ISRCTN registry, ISRCTN42686094.

Role of the funding source
The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between July 22, 2014, and Sept 3, 2022, 101 children were assessed for eligibility to the trial, of whom 45 met inclusion criteria and were enrolled. Eight centres in seven countries (Denmark [n=3], Finland [n=5], France [n=4], Germany [n=2], the Netherlands [n=29], Spain [n=1], and the UK [n=1]) took part in the study, but initially, principal investigators at 21 tertiary referral centres intended to participate. However, complying with regulatory and bureaucratic requirements proved to be practically unfeasible for some centres, and five sites were never initiated. Although pretrial feasibility survey results suggested that more than sufficient numbers of participants (1–5 per year per site) would meet the inclusion criteria, actual recruitment at centres was hampered for many reasons, including parental or physician's treatment preferences, or referrals made later than 6 months after the EE-SWAS diagnosis. In addition, for many sites, it was not feasible to schedule a whole-night EEG and neuropsychological assessment at short notice, often leading to the start of treatment with either corticosteroids or clobazam before a participant could be enrolled in the trial. Eventually, only eight sites enrolled participants. The trial steering committee regularly monitored and discussed the progress of the trial and decided unanimously on Dec 17, 2021—after a plateau of recruitment at 45 participants in 7 years had been reached—that completion of the trial with the predefined required number of 130 participants was not feasible. The accredited ethics committee and competent authorities were notified about the premature termination of the trial.

Of the 45 participants who were enrolled, 22 were randomised to receive corticosteroids and 23 to receive clobazam (figure; Baseline demographic and clinical characteristics were generally similar across treatment groups (table 1). Age at EE-SWAS diagnosis and age at first seizure were higher in the corticosteroid group. In the corticosteroid group, 18 participants received pulsed methylprednisolone (dose according to protocol) and four received oral prednisolone therapy (mean dose after 6 months was 1·5 mg/kg per day, SD 0·4). After 6 months of treatment, the mean dose of clobazam was 0·6 mg/kg per day (SD 0·3). No new concomitant antiseizure medications were started during the first 6 months of the trial. Of the 22 children assigned corticosteroids, five discontinued treatment by 6 months and switched to clobazam; a further 14 discontinued treatment by 18 months, of whom one switched to clobazam and 13 either started another treatment or stopped treatment. Of the 23 children assigned clobazam, two discontinued treatment by 6 months and switched to corticosteroids; a further three discontinued treatment by 18 months, of whom two switched to corticosteroids and one started another treatment or stopped treatment was still ongoing at 6 months for 17 children assigned corticosteroids (one of whom was also taking clobazam) and for 19 children assigned clobazam (two of whom were also taking corticosteroids). At 18 months, treatment was ongoing for two children assigned corticosteroids (one of whom was also taking another treatment) and for 16 children assigned clobazam (two of whom were also taking another treatment).

Two participants, both in the clobazam group, dropped out after 1 month, in one case due to adverse events (behavioural problems, especially aggressive behaviour) and in the other case for unknown reasons. It was impossible to asses the total IQ at 6 months in all participants, so the IQ responder rate could only be assessed in 38 participants. The cognitive sum score responder rate could be assessed in all 43 participants. The IQ responder rate at 6 months was 25% (five of 20 participants with improvement of ≥11·25 IQ points) in the corticosteroid group compared with 0% (none of 18) in the clobazam group (RR 10·0, 95% CI 1·2–1310·4; p=0·025; table 2). The cognitive sum score responder rate at 6 months was 5% in both the corticosteroid group (one of 22) and the clobazam group (one of 21; RR 1·0, 95% CI 0·1–11·7; p=0·97). Sensitivity analyses showed similar results (appendix pp 4–5)

Secondary outcomes at both 6 months and 18 months did not differ between the two treatment groups, except for mean delta IQ at 6 months (table 2). Children assigned corticosteroids improved on average by 4·9 IQ points compared with baseline, whereas children treated with clobazam

showed a decline by 0·7 IQ points (β 5·6, 95% CI 0·3–10·8, p=0·039). On multivariable regression analysis an unknown aetiology for EE-SWAS was found to be predictive of a higher delta IQ (β 8·8, 95% CI 3·1–14·5; p=0·0036) and of a higher delta cognitive sum score (0·3, 0·0–0·6; p=0·041). The predictive value of the multivariable models was relatively low for delta IQ (adjusted R^2 0·18) and delta cognitive sum score (adjusted R^2 –0·02) (appendix p 6).

Ten (45%) of 22 participants in the corticosteroid group had at least one adverse event after 6 months versus 11 (52%) of 21 in the clobazam group (RR 0·8, 95% CI 0·4–1·4; p=0·65; table 3). The most frequently reported adverse event was fatigue in the clobazam group (five [24%] of 21) and weight gain in the corticosteroid group (three [14%] of 22). Three serious adverse events were recorded, two in the clobazam group (hospitalisation due to seizure aggravation in one case and due to respiratory tract infection in the other case) and one in the corticosteroids group (hospitalisation due to laryngitis). All serious adverse events resolved without sequelae. One adverse event was reported between 6 months and 18 months (fever in clobazam group).

Discussion

Our multicentre randomised controlled trial with blinded outcome assessment is the first trial to compare cognitive outcomes in children with EE-SWAS taking two of the most commonly prescribed treatments for the disorder. However, the trial was terminated prematurely for feasibility reasons, and the target sample size was not met, so findings must be interpreted with caution]. Our data provide an indication that corticosteroids might be more effective than clobazam in improving IQ outcomes (both in terms of responder rates and changes in scores) in children with EE-SWAS who start treatment within 6 months of diagnosis. 25% of participants assigned to corticosteroids showed a marked improvement in IQ (>11·25 points) after 6 months of treatment compared with 0% in the clobazam group. Over the same period, children who were started on treatment with corticosteroids improved on average by 4·9 IQ points compared with baseline, whereas children treated with clobazam showed a decline by 0·7 IQ points. These findings support those of previous smaller and retrospective studies in children with EE-SWAS, in which early treatment with steroids was suggested to be more effective than treatment with clobazam.[11]

The significantly higher IQ responder rate (proportion of children with an improvement of over 11·25 IQ points) at 6 months can be considered clinically relevant.[12] However, the clinical relevance of the average IQ change is less certain, and corticosteroids did not differ from clobazam in improving cognitive sum score outcomes (for both responder rates and changes in scores), which are a measure of overall cognitive functioning. This finding could be accounted for by the difficulty in comparing cognitive or behavioural progression in this heterogeneous population with global scores, because it might level out individual differences. Because the cognitive sum score is based on several different tests, this score might be less sensitive to change than IQ scores. Subjective improvement in daily functioning, as measured by VAS scores, also did not differ significantly between treatment groups, but parents and treating physicians determined that most participants had improved when compared with baseline. Overall, these results clearly indicate that more effective therapies for this condition are needed.

At 18 months, differences in IQ responder rates and delta IQ were not different between the two treatment groups, which could be because IQ data were only available for two-thirds of participants in total (31 [69%] of 45). In addition, clinical management after 6 months was at the treating physician's discretion and was highly variable across individuals, which might have obscured differences in effectiveness between the treatments allocated initially. Specifically, at 18 months only two (10%) of 21 children initially randomised to corticosteroids and available for assessment remained on corticosteroid treatment, compared with 16 (76%) 21 who were randomly assigned to clobazam and still on that treatment. Corticosteroid treatment is often given for a limited period,

since it targets inflammation which is considered to have largely resolved after 6 months, and to prevent long term adverse events. Clobazam is often continued for years if considered (partly) effective and well tolerated.

Only a few participants in each treatment group showed a major improvement in EEG spike-wave discharges, which was a post-hoc analysis. At 6 months, seven (32%) of 22 participants in the corticosteroid group no longer met criteria for EE-SWAS (arbitrarily defined as SWI during sleep <50%), compared with three (14%) of 21 in the clobazam group, a difference that was not statistically significant. In previous retrospective studies, higher EEG response rates had been reported with steroids compared with benzodiazepines.[11,14] We did not find a relationship between change in IQ and improvement of EEG, consistent with earlier studies.[11,20] Of note, the effect of corticosteroids on IQ measures might be related to mechanisms other than suppression of spike-wave EEG activity. According to the synaptic homoeostasis hypothesis, cognitive and behavioural problems in EE-SWAS might be related to impaired synaptic downscaling during sleep and, consequently, failure to provide the conditions for an increase in synaptic connections during the following day.[21] Previous research has shown that synaptic downscaling is disturbed by epileptiform activity in EE-SWAS and that cognitive and behavioural problems in children with EE-SWAS correlate with a reduced decrease in slow wave slope in overnight sleep EEG (a measure for synaptic downscaling).[22,23] Treatment with corticosteroids might affect slow-wave homoeostasis. Another hypothesis ascribes the effect of corticosteroids on cognition via inhibition of immune-mediated and inflammatory mechanisms.[24,25] This study underlines the need to further investigate the exact relationship—cause, consequence, or epiphenomenon—between EE-SWAS and inflammation.

An unknown aetiology for EE-SWAS was identified in a prespecified multivariable analysis as an independent predictor of a favourable treatment effect on IQ and cognitive sum scores. Better outcomes have been previously reported in children with an unknown cause for EE-SWAS, compared with those with a structural or genetic cause for the disorder, except for those who were surgically treated.[11] Unlike previous studies, we did not find an association between baseline cognitive function (as assessed by IQ and cognitive sum score) and treatment efficacy.[14,26] Although it has been suggested that a favourable outcome in children with EE-SWAS correlates with shorter duration of the regression period,[12] neither the time interval between recording of the SWAS pattern and inclusion nor the number of pharmacological treatments tried before diagnosis was related to improved outcomes in our study. This finding could be accounted for by the fact that only children diagnosed recently (within 6 months) were eligible for this trial.[11]

Our study has several limitations.[27] First, we did not reach the targeted sample size, which affects the robustness of the conclusions that can be drawn from the analysis of primary and secondary outcome measures. Second, participants and treating physicians were not masked to treatment, which could have led to biased evaluation of our subjective outcome measure global daily functioning, assessed by VAS score. In both treatment groups, more than 70% of parents reported improved cognitive functioning in their child after 6 months, reflected by a positive VAS score. This favourable subjective assessment was not associated with equally high improvement rates in objective measures, eg NPA, suggesting that reports from parents might have been biased by over-expectation of treatment effects. It is known that non-masked participants might exaggerate treatment effects, caused by expectations of treatment effect or by justification of the (invasive) treatment they were subjected to in the first place.[28,29] Alternatively, other outcome measures (eg, patient-centred outcome measures) could better indicate clinically relevant outcomes. Third, two different administration regimens (oral prednisone and intravenous methylprednisolone pulse therapy) were permitted in the corticosteroid group. Because of the small sample size, potential differences in efficacy and safety between these regimens could not be assessed meaningfully.

In conclusion, we have shown that initiating treatment for EE-SWAS with corticosteroids might improve IQ outcomes after 6 months compared with starting treatment with clobazam. No major difference in adverse event rates was found. Because of the many challenges faced during this trial, and the disappointing enrolment rate, it is unlikely that a comparable trial with a larger number of participants can be successfully done in the future. Our findings complement those from earlier uncontrolled studies and support the early use of corticosteroids in the treatment of children with EE-SWAS.

RESCUE ESES study group

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Contributors

BvdM, FEJ, and KPJB initiated the study and contributed to study design, selection of participating centres, acquisition of funding, acquisition of grants, acquisition of ethical approval, protocol development, and data collection. MMLvA, BvdM, FEJ, and KPJB contributed to trial coordination, data management, verification of the data, data interpretation, statistical analysis, and writing of the manuscript. AA, EP, HCvT, and FSSL contributed to study design, data interpretation, and critical review of the manuscript. AA, LM, GR, MSK, AdS-M, KAK, JJ, JHC, and IGM contributed to data collection and critical review of the manuscript. MMLvA and WMO contributed to the statistical analysis. The RESCUE ESES study group participated in the execution of the trial. All authors read and approved the final manuscript. All authors vouch for the completeness and accuracy of the data and analyses, for the reporting of the trial results and adverse events, and for the adherence of the trial conduct to the protocol. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

We support data sharing within the restrictions of the ethical approval permissions. Requests can be made to the corresponding author.

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Figure: Trial profile
ITT=intention to treat. IQ=intelligence quotient