Vigabatrin with hormonal treatment versus hormonal treatment alone (ICISS) for infantile spasms: 18-month outcomes of an open-label, randomised controlled trial

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Summary

Background Infantile spasms constitute a severe form of epileptic encephalopathy. In the International Collaborative Infantile Spasms Study (ICISS), we showed that combining vigabatrin with hormonal therapy was more effective than hormonal therapy alone at stopping spasms between days 14 and 42 of treatment. In this planned follow-up, we aimed to assess whether combination therapy was associated with improved developmental and epilepsy outcomes at 18 months of age.

Methods In ICISS, a multicentre, open-label, randomised controlled trial, infants were enrolled from 102 hospitals (three in Australia, 11 in Germany, two in New Zealand, three in Switzerland, and 83 in the UK). Eligible infants had a clinical diagnosis of infantile spasms and a hypsarrhythmic (or similar) electroencephalogram (EEG) no more than 7 days before enrolment. Participants were randomly assigned (1:1) by a secure website to receive hormonal therapy with vigabatrin or hormonal therapy alone. If parents consented, there was an additional randomisation (1:1) of type of hormonal therapy used (prednisolone or tetracosactide depot). Block randomisation was stratified for hormonal treatment and risk of developmental impairment. Parents and clinicians were not masked to therapy, but investigators assessing epilepsy and developmental outcomes at 18 months were masked to treatment allocation. Minimum doses were oral prednisolone 10 mg four times a day or intramuscular tetracosactide depot 0·5 mg (40 IU) on alternate days with or without oral vigabatrin 100 mg/kg per day. The primary outcome at 18 months was development as assessed by the Vineland Adaptive Behaviour Scales (VABS) composite score. Secondary outcomes were the presence or absence of epileptic seizures or infantile spasms in the previous 28 days, as recorded by parents and carers, and the use of any anti-epileptic treatment (including ketogenic diet) in the previous 28 days. Analysis was by intention to treat. The trial is registered with the ISRCTN registry, number 54363174, and EudraCT, number 2006-000788-27.

Findings Between March 7, 2007, and May 22, 2014, 766 infants were screened and, of those, 377 were randomly assigned to hormonal therapy with vigabatrin (n=186) or hormonal therapy alone (n=191). 362 infants were assessed for developmental and epilepsy outcomes at 18 months, 181 in each treatment group. Mean VABS scores did not differ significantly between the combination therapy group and the hormonal therapy alone group (73·9 [SE 1·3] *vs* 72·7 [1·4], difference –1·2 [95% CI –4·9 to 2·6], p=0·55). Presence of epilepsy at the assessment at age 18 months was similar in both treatment groups (54 [30·0%] of 180 infants who received combination therapy *vs* 52 [29·2%] of 178 who received hormonal therapy alone; difference 0·8% [95% CI –8·8 to 10·4], p=0·90). Presence of spasms was also similar in both treatment groups (27 [15·0%] of 180 infants on combination therapy *vs* 28 [15·7%] of 178 on hormonal therapy alone; difference 0·7% [95% CI –6·9 to 8·3], p=0·85) . At the 18-month assessment, 158 (44·1%) of 358 infants were on some form of anti-epileptic treatment. Initial control of spasms between days 14 and 42 of treatment was associated with higher mean VABS scores at 18 months (79·1 [SE 1·2] *vs* 63·2 [1·1], difference 15·9 [95% CI 12·4 to 19·5], p<0·001) and with higher likelihood of absence of seizures at 18 months (in 39 [17·0%] of 229 infants who achieved spasm cessation *vs* 67 [51·9%] of 129 who did not; difference 34·9% [24·8 to 45·0], p<0·001). Increasing lead-time to treatment was associated with lower VABS scores (analysis of variance: $F[4,354]=6·38$, p<0·001) and worse epilepsy outcomes (p=0·023).

Interpretation Combination therapy did not result in improved developmental or epilepsy outcomes at 18 months. However, early clinical response to treatment was associated with improved developmental and epilepsy outcomes at 18 months. Longer lead-time to treatment was associated with poorer outcomes. Rapid diagnosis and effective treatment of infantile spasms could therefore improve outcomes.

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See Online for appendix

Research in context

Evidence before this study

We did a Cochrane systematic review into the treatment of infantile spasms that we have continued to update up to April, 2018. We searched the Cochrane Epilepsy Group Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (January, 1946, to April, 2018), Embase (January, 1980, to March, 2003), ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform (ICTRP), and reference lists of all retrieved articles. We found 20 small randomised controlled trials (fewer than 100 patients enrolled) and three larger randomised controlled trials (more than 100 patients enrolled) that looked at 12 different pharmaceutical agents. Overall, the methodological quality of the published studies has been poor. The most popular and commonly used treatment modalities are either hormonal treatments (prednisolone, natural or synthetic adrenocorticotropic hormone) or vigabatrin. The strongest evidence before this study suggested that hormonal therapy (prednisolone or tetracosactide depot) led to resolution of spasms faster and in more infants than vigabatrin. The same study suggested that hormonal treatments might improve long-term neurodevelopmental outcomes compared with vigabatrin in infants in whom no underlying cause for their spasms could be found. The study also provided evidence that longer lead-times to treatment were associated with worse developmental outcomes when measured at 4 years. The initial results from our study, published in 2016, suggest that a combination of hormonal treatment (prednisolone or tetracosactide depot) and vigabatrin leads to resolution of spasms faster and in more infants than does hormonal therapy alone.

Added value of this study

The International Collaborative Infantile Spasms (ICISS) study is, to our knowledge, the largest treatment trial of infantile spasms up to May 1, 2018. It is the first study to assess a combination of therapies (hormonal therapies plus vigabatrin) versus the current therapeutic modality and provides evidence for their effectiveness at stopping spasms between days 14 and 42 of treatment. The results of the 18-month follow-up data show that early clinical response to therapy, low risk of developmental impairment at randomisation, and shorter lead-times to treatment are all associated with improved developmental and epilepsy outcomes at 18 months. However, the study does not show any difference in developmental or epilepsy outcomes at 18 months between combination therapy and hormonal therapies alone.

Implications of all the available evidence

ICISS suggests a modality of treatment that will stop spasms faster and in more children than has previously been achieved with existing treatment strategies. The study has not shown that this treatment modality is associated with improved developmental and epilepsy outcomes at 18 months. However, it has shown that early response to treatment and shorter lead-times to treatment are associated with better long-term outcomes and implies that rapid diagnosis and effective treatment of infantile spasms is important in achieving improved outcomes in these patients.

Introduction

Infantile spasms are a severe form of epilepsy often associated with a poor outcome both with respect to development and future epilepsy control.[1–3] They were the first described form of epileptic encephalopathy—a condition in which the epileptic activity itself contributes to cognitive and neurological decline.[4] These spasms are also the most prevalent form of epileptic encephalopathy, affecting approximately one in 2500 infants.[5] Effective treatment that shortens the duration of epileptic encephalopathy could lead to better developmental and epilepsy outcomes.

We have previously shown in the International Collaborative Infantile Spasms Study (ICISS) that combination treatment with vigabatrin and hormonal therapy (either prednisolone or tetracosactide depot) is more effective than hormonal therapy alone at both stopping spasms (between days 14 and 42 of treatment inclusive) and achieving an electroclinical response.[6] We hypothesised at the beginning of the trial that more effective treatment would also be associated with better developmental and epilepsy outcomes at 18 months of age. In particular, as was shown in the earlier United Kingdom Infantile Spasm Study (UKISS),[7] we thought this effect would be most clearly seen in those children who had no obvious underlying cause for their infantile spasms, since these children have no known reason for poor development other than their spasms.[7] Here, we report the developmental and epilepsy outcomes of infants from the ICISS trial as they reached 18 months of age.

For the **study protocol** see www.iciss.org.uk

Methods

Study design

ICISS was a pragmatic, multicentre, parallel-group, open-label, randomised controlled trial with some masked outcome measures. Infants were enrolled from 102 hospitals (three in Australia, 11 in Germany, two in New Zealand, three in Switzerland, and 83 in the UK). Local investigators enrolled and managed patients and collected information related to cessation of spasms. Treatment allocation was done from the trial website. Our research protocol was approved by the UK South West Multicentre Research Ethics Committee (06/MRE06/21) and all relevant local research ethics committees.

The full study protocol is available online.

Participants

Inclusion criteria were a clinical diagnosis of infantile spasms by the local investigator and an electroencephalogram (EEG) that was judged by local neurophysiologists to be hypsarrhythmic or similar, compatible with the diagnosis of infantile spasms. Exclusion criteria were age younger than 2 months or older than 14 months; a delay of more than 7 days since diagnosis; a diagnosis of tuberous sclerosis; previous treatment for infantile spasms or previous use of hormonal treatments or vigabatrin; the co-incidence of another condition likely to be lethal before outcome assessment; predictable lack of availability for follow-up to 18 months; and difficulty with language used for assessment or participation in a concurrent trial. Pyridoxine could be given to exclude pyridoxine-dependent seizures but not as an independent treatment intervention for infantile spasms. Written informed consent was obtained from parents or a guardian.

Randomisation and masking

Patients were randomly assigned centrally by use of an interactive computer system accessed independently by recruiting clinicians via the trial website. Patients were allocated in a 1:1 ratio to receive combination therapy or hormonal therapy alone. Where parents consented, there was an additional randomisation of type of hormonal therapy used, prednisolone or tetracosactide depot, in a 1:1 ratio. Block randomisation (random block size <10) was used and investigators were masked to actual block size. Randomisation was stratified on two variables: presence or absence of factors that would increase the risk of developmental impairment (one or more of: chromosomal abnormality or clinical syndrome, neonatal encephalopathy with seizures, and cerebral palsy or developmental impairment diagnosed before onset of spasms); and hormonal treatment (prednisolone or tetracosactide depot) randomly allocated or chosen by parents. An independent statistician generated the allocation sequences.

Cause of infantile spasms was ascertained by FJKO'C and JPO, who were masked to treatment allocation, by use of information available from clinical history, examination, and investigations. The cause was classified as proven, no cause identified, or cause not known if a major piece of information was missing. ML reviewed MRI scans.

Procedures

The study treatments were prednisolone (soluble prednisolone tablets; Sovereign Medical, Basildon, UK), tetracosactide depot (Synacthen Depot; Alliance Pharmaceuticals, Chippenham, UK), and vigabatrin (Sabril; Aventis Pharma, West Malling, UK). The same products were used outside the UK and, although the market authorisation holder varied, this designation did not affect the dose and drugs used. Prednisolone was given orally (10 mg four times a day) for 2 weeks. If spasms continued on day 7 or reappeared between day 8 and day 14 inclusive, the dose was increased to 20 mg three times a day for the remaining doses. Tetracosactide depot was given intramuscularly (0·5 mg [40 IU] on alternate days) for 2 weeks. If spasms continued on day 7 or reappeared between day 8 and day 14 inclusive, the dose was increased to 0·75 mg on alternate days for the remaining doses. Vigabatrin was given orally in two divided doses per day (50 mg/kg per day for the first two doses, increasing to 100 mg/kg per day after 24 h and, if spasms continued after a further 72 h, to 150 mg/kg per day). After 2 weeks of treatment, hormonal therapy was tapered: all children received a reducing dose of prednisolone with reductions of 10 mg every 5 days or, if on the higher dose of treatment, 40 mg daily, then 20 mg, then 10 mg for 5-day periods. Hormonal therapy ceased after day 29. Vigabatrin was continued at the same dose on a bodyweight basis until 3 months from the start of treatment when the dose was reduced over 4 weeks. Local investigators were allowed to change treatment if this was considered to be in the infant's best interest, and in non-responders. Drug accountability was monitored by directly asking parents or guardians.

Parents or carers filled in a daily record of spasm frequency for the first 42 days of the trial and there was a mandated minimum schedule of outpatient follow-up appointments with treating clinicians on days 15 and 43. After day 43, infants were reviewed according to clinical need. The protocol requested 3-monthly reports, including one at 18 months of age, providing information about spasms since the last assessment, treatment with trial medications, adverse reactions, and further investigations for underlying causes. A structured paediatric epilepsy history was taken at 18 months of age by assessors who were masked to initial treatment allocation (AAM in Australia, New Zealand, and the UK; FDA in Germany and Switzerland) that recorded, with respect to the previous 28 days, the presence or absence of infantile spasms, the presence or absence of any other type of epileptic seizure, and the use of any anti-epileptic medication or ketogenic diet, or both. Any history of epilepsy surgery (including vagal nerve stimulation) was also noted.

Lead-time to initial treatment for infantile spasms was recorded. Lead-time refers to the delay between clinical onset of spasms and initiation of treatment (figure 1), and was categorised into five time periods (≤7 days, 8–14 days, 15–28 days, 29 days to 2 months, and >2 months) or as not known. Clinical onset of spasms precedes (often by days or weeks) formal diagnosis of infantile spasms, which requires physician assessment and EEG confirmation (figure 1).

Development was investigated by an assessor (AAM in Australia, New Zealand, and the UK; FDA in Germany and Switzerland) who was masked to treatment allocation, by means of telephone interview with a parent

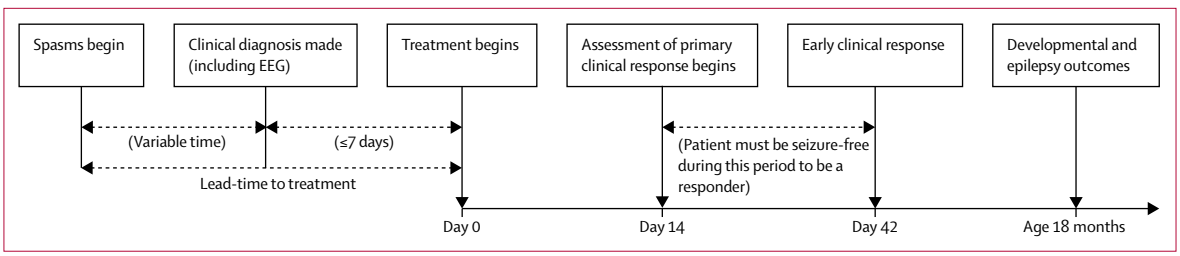

Figure 1: **Clinical trial pathway**
EEG=electroencephalogram.

when their child was 18 months of age. Development was assessed with the Vineland Adaptive Behaviour Scales (VABS), which examine adaptive behaviour in four domains—communication, daily living skills, socialisation, and motor skills—from which a composite score is derived. In a healthy reference population the VABS yields a mean score of 100 (SD 15).

Outcomes

The primary early outcome was cessation of spasms, which was defined as no witnessed spasms on and between day 14 and day 42 inclusive from trial entry, as recorded by parents or carers in a seizure diary. The primary late outcome was development at 18 months of age, as measured by the VABS composite score. Secondary outcomes at 18 months were the presence or absence of infantile spasms in the preceding 28 days, the presence or absence of any form of epileptic seizure in the previous 28 days, and the use of any anti-epileptic treatment (including ketogenic diet) in the previous 28 days.

Adverse events were assessed by the local investigator and only adverse reactions were reported to the trial centre. An adverse reaction was defined as any untoward or unintended response thought to be related to trial treatments. An adverse reaction was judged to be serious if it was life-threatening, caused death, resulted in persistent or significant disability, or required admission to hospital. Causality was ascertained by the treating clinician. Expected adverse reactions were listed in the protocol. During and immediately after hormonal treatment, the use of antibiotics, including an anti-staphylococcal agent, was recommended for treatment of fever. Central monitoring of data was done by JPO, FJKO'C, and SWE, who reviewed the case report forms as they were returned to the trial centre in Bath, UK.

Statistical analysis

The target number for patients in the trial had been ascertained by the power calculation done to see a difference in both the early primary outcome (ie, cessation of spasms) and the late primary outcome (ie, development at 18 months). Data from our previous clinical trial (UKISS) had shown that a difference in development between the two treatment groups was only found in the subgroup with no identified cause.[7] In this group, the VABS composite score was 88 for those on hormonal treatments alone and we judged that this score would need to improve by approximately half a standard deviation (ie, 7 points) on combination therapy to be considered clinically meaningful. Consequently, we calculated that the number of patients required to see an improvement in mean VABS composite score from 88 to 95 in the subgroup with no identified cause, with a two-tailed significance level of 0·05 and 90% statistical power, would be 96 in each group or 72 in each group at 80% power. Recruitment commenced on March 7, 2007, and by May 22, 2014, 377 infants had been recruited, thus exceeding the requirements for 80% power for the early primary outcome and the late primary outcome. The decision was then taken to halt recruitment, given the disproportionate costs and renewed applications for funding that would be required to extend the trial to recruit the number of patients needed to reach 90% power.

All analyses were done under the intention-to-treat principle. The primary explanatory variable of interest was the effect of treatment modality. We also anticipated that initial response to treatment (ie, absence of spasms between day 14 and day 42), lead-time to treatment of spasms, presence of an underlying cause, and age at randomisation were a priori likely to influence both the developmental and epilepsy-related outcomes. Additionally, we thought that the presence of continuing epilepsy at 18 months might explain some of the variation in developmental scores. Differences in VABS composite scores were initially compared with two-sample *t* tests for categorical variables and either ANOVA or linear regression for continuous explanatory variables. We tested the assumptions of normality using the Shapiro-Wilk test and homogeneity of variances with Bartlett's test. Multivariable analyses controlling for the design factors of the study (ie, risk of developmental impairment, type of hormonal treatment, and whether or not hormonal treatment was randomised) and other variables that were significantly associated with the main outcome variable on univariable analyses were done by fitting multivariable linear regression models. Goodness of fit of models was compared with the Bayesian information criterion.

For the secondary outcomes at age 18 months (ie, presence of infantile spasms, presence of epileptic seizures at 18 months, and use of anti-epileptic treatment at 18 months) differences in proportions were analysed with Pearson's χ^2 tests. Results are summarised as treatment differences and 95% CI. Sensitivity analyses controlling for the design factors of the study and other variables significantly associated with the secondary outcomes were done by fitting logistic regression models. These models were not over-fitted.[8] Statistical analyses were done with Stata IC, version 11.2, and R, version 3.4.2.

The trial is registered with the ISRCTN registry, number 54363174, and the EudraCT, number 2006-000788-27.

Role of the funding source

The sponsor and funding sources of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. FJKO'C, JPO, SWE, and MCB had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between March 7, 2007, and May 22, 2014, 766 infants were screened. From the original cohort, 362 (96%) of 377 infants underwent developmental assessment with the VABS (figure 2). No clinically important imbalances were observed between treatment groups with regard to baseline characteristics (appendix). 299 (83%) of the remaining cohort underwent assessment in their 18th month, and 352 (97%) had been assessed by the end of their 19th month. Ten infants were assessed after the 19th month: five at 20 months, two at 22 months, one at 23 months, one at 25 months, and one at 32 months. 181 infants had received hormonal therapy alone and 181 had received hormonal therapy with vigabatrin. Of the 15 infants who did not have an 18-month assessment, seven had died, six were lost to follow-up, and two withdrew from the study (figure 2). The acute causes of death in the seven infants who died were documented as: respiratory failure secondary to mitochondrial disorder, macrophage activation syndrome, aspiration pneumonia, respiratory failure secondary to presumed brainstem dysfunction, cardiopulmonary arrest secondary to undiagnosed neurodegenerative disorder, hepatic failure and metabolic acidosis, and pneumonia. After analysis of the trial clinical report forms and neuroimaging, the underlying cause of infantile spasms was proven in 209 (58%) infants and no cause was identified in 153 (42%) infants in the cohort that was followed up at 18 months.

Data on epilepsy outcomes were available for 358 (95%) of the original cohort of 377 infants. Two infants who had developmental assessments did not provide epilepsy histories at 18 months, and for two other infants the history and the epilepsy questionnaire did not clarify whether epileptic seizures were present.

VABS composite scores in the cohort ranged from 44 to 138 (mean 73·3 [SD 18·2]). Mean composite scores were higher in those infants judged to be at low risk of developmental impairment at randomisation than in those at high risk (84·6 [SE 1·3] *vs* 63·9 [0·9], difference 20·7 [95% CI 17·6–23·8], p<0·001). Composite scores were also higher in those infants who had achieved a primary clinical response (ie, cessation of spasms between day 14 and day 42 inclusive) than in those who had not (79·1 [SE 1·2] *vs* 63·2 [1·1], difference 15·9 [95% CI 12·4–19·5], p<0·001).

VABS mean composite scores did not differ significantly between the combination therapy group and the hormonal therapy alone group (73·9 [SE 1·3] *vs* 72·7 [1·4], difference –1·2 [95% CI –4·9 to 2·6], p=0·55). Even after stratifying the data by risk of developmental impairment, VABS scores did not differ significantly between the treatment groups. In children at high risk of developmental impairment at randomisation, the mean VABS composite scores in the combination therapy group were 63·6 (SE 1·2) compared with 64·1 (1·4) in the

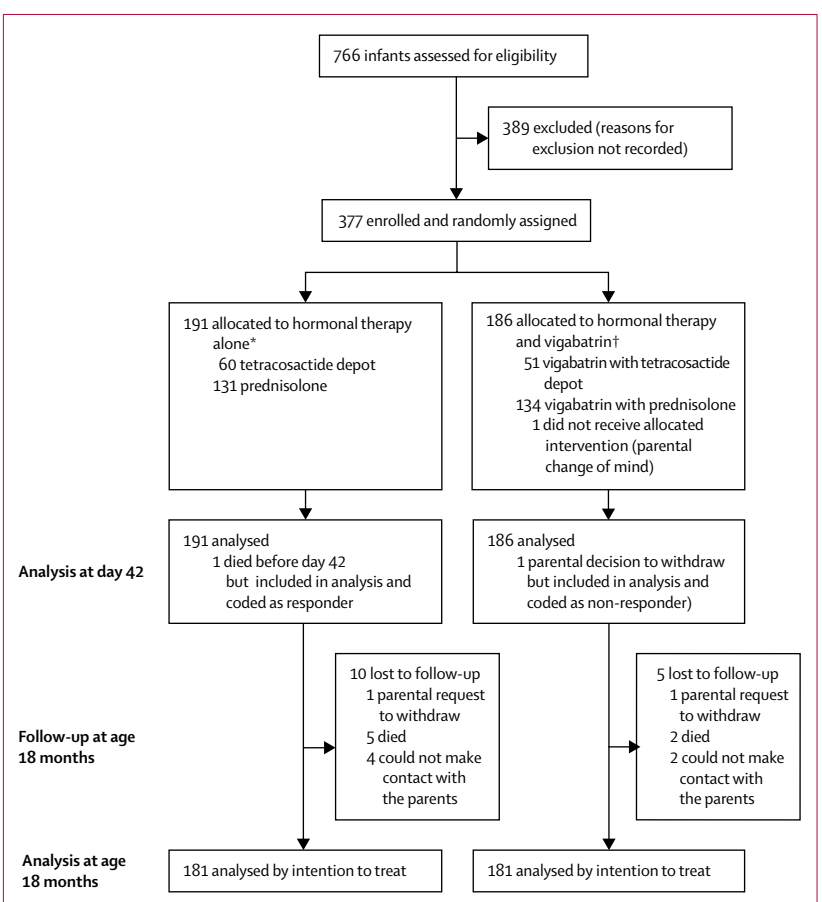

Figure 2: **Trial profile**

*In the hormonal therapy alone group, three patients also received vigabatrin and nine had incomplete compliance (eg, did not receive the recommended dose). †In the hormonal therapy and vigabatrin group, ten patients had incomplete compliance (eg, did not receive the recommended dose).

hormonal therapy alone group (difference 0·5 [95% CI −3·1 to 4·1], p=0·79). In children at lower risk for developmental impairment the mean scores in the combination therapy group were 86·5 (SE 1·8) and those in the hormonal therapy alone group were 82·7 (2·0; difference −3·8 [95% CI −9 to 1·5], p=0·15). Similarly there was no interaction between treatment modality and cause with respect to VABS composite scores. The mean VABS score in the group with no cause identified for those on combination therapy was 83·5 (SE 2·1) compared with 81·5 (2·1) for those receiving hormonal therapy alone (difference −2·0 [95% CI −7·9 to 4·0], *t*=−0·7, p=0·52). The associations between explanatory variables and VABS scores are summarised in the appendix.

	Coefficient	95% CI	p value
Treatment modality	0·66	−2·0 to 3·4	0·63
Risk of developmental impairment	−14·1	−17·4 to −10·9	<0·001
Proven underlying cause	−5·0	−8·2 to −1·8	0·002
Hormone randomised	0·75	−2·2 to 3·7	0·62
Early clinical response	7·2	4·1 to 10·3	<0·001
Lead time	−1·5	−2·5 to −0·57	0·002
Current epilepsy	−11·7	−14·9 to −8·5	<0·001
Type of hormonal treatment	0·11	−3·0 to 3·2	0·95
Constant	86·3	80·6 to 91·9	<0·001

*Lead-time to treatment not recorded in three infants and epilepsy outcome not recorded in four infants.

Table 1: **Results of final multiple linear regression with Vineland Adaptive Behaviour Scale as dependant variable***

	High risk of development impairment	Low risk of development impairment	Whole group	p value	Total VABS score
<7 days	66·5 (15·7)	88·7 (17·2)	78·2 (19·8)		104
8–14 days	69·5 (13·8)	85·0 (17·1)	77·3 (17·3)	0·73	66
15–28 days	63·9 (10·9)	81·0 (18·3)	72·3 (17·2)	0·03	79
29 days to 2 months	59·7 (10·4)	84·8 (15·0)	68·8 (17·2)	0·001	58
>2 months	59·5 (9·3)	78·9 (15·8)	65·5 (14·6)	<0·001	52

Data are mean (SD), unless otherwise stated. Analysis of variance: $F(4,354)=6{\cdot}38$, p=0·0001. VABS=Vineland Adaptive Behaviour Scale. *Lead-time to treatment not recorded in three cases.

Table 2: **Lead-time to treatment and mean VABS composite scores at 18 months***

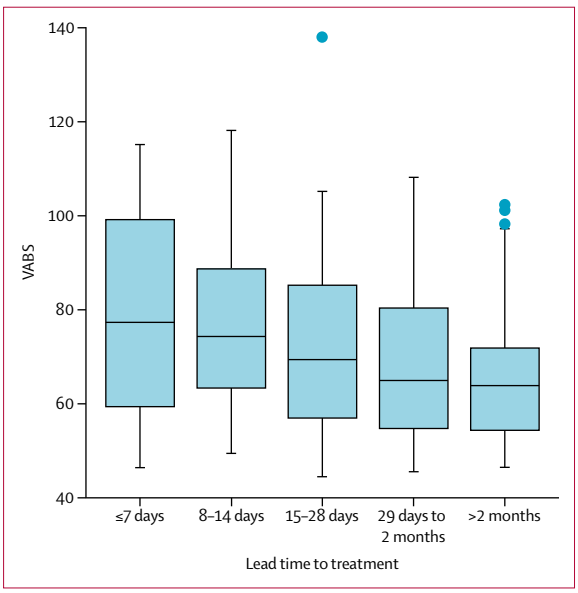

Figure 3: **Box and whisker plots showing the distribution of VABS composite scores**
VABS=Vineland Adaptive Behaviour Scale. Circles represent outlying observations.

The absence of any treatment effect on VABS scores remained in the sensitivity analysis, with multiple linear regression, taking into account the design factors of the study (ie, controlling for risk of developmental impairment, type of hormone treatment, and whether or not hormonal treatment was randomised) and the other explanatory variables strongly associated with the outcome (ie, early clinical response, lead-time to treatment, presence of an underlying cause, and continuing epilepsy at 18 months; table 1). In the multivariable analysis, risk of developmental impairment, early clinical response, lead-time to treatment, presence of an underlying cause, and continuing epilepsy at 18 months remained significant independent predictors of developmental outcome.

Increasing lead-time to treatment was related to mean VABS composite scores, with each increase in lead-time category being associated with a decrease in composite score (table 2; figure 3). Increasing lead-time to treatment was also associated with the risk of developmental impairment, with infants at high risk of impairment at randomisation having longer lead-times to treatment than those with low risk of developmental impairment at randomisation (appendix).

The presence of an underlying cause was associated with a lower mean VABS composite score than was absence of an identified cause (66·8 [SE 1·0] *vs* 82·5 [1·5], difference 15·7 [95% CI 12·2–19·2], p<0·001). The presence of current epileptic seizures at 18 months was also associated with lower VABS composite scores than was absence of epileptic seizures at the same timepoint (60·5 [SE 1·1] *vs* 79·0 [1·1], difference 18·5 [95% CI 14·8–22·2], p<0·001).

VABS scores were also related to age (in days) at randomisation (coefficient −0·06 [SE 0·013] p<0·001), with each 1-day increase in age at randomisation being associated with a drop of 0·06 points on the VABS scale. Age at randomisation was associated with the risk of developmental impairment assessed at time of enrolment into the trial. The mean age at randomisation was 233 days (SE 5·6) in the high-risk group versus 197 days (4·6) in the low-risk group (mean difference 35·9 [95% CI 50·4–21·3], p<0·0001). Age at randomisation was also linearly related to lead-time to treatment, with each increase in lead-time category being associated with an increase in age at randomisation of 16·6 days (coefficient

16·6 [SE 2·6], p<0·001). The association between VABS score and age at randomisation disappeared completely when controlling for risk of developmental impairment and lead-time to treatment.

Epileptic seizures of any type at 18 months were seen in 106 (30%) of 358 infants. Seizures were seen in 39 (17·0%) of 229 infants who had achieved a primary early clinical response and in 67 (51·9%) of 129 who had not achieved spasm cessation (difference 34·9% [95% CI 24·8–45·0], p<0·001).

Epileptic seizures were seen in 72 (36·9%) of 195 infants who were at high risk of developmental impairment at randomisation and in 34 (20·9%) of 163 at low risk (difference 16% [95% CI 6·4–25·6], p=0·001). Similarly, seizures were seen in 72 (35%) of 206 infants who had a proven cause and in 34 (22·4%) of 152 with no cause identified (difference 12·6% [95% CI 2·8–24·4], p=0·01).

Longer lead-time to treatment was associated with a linear trend of higher proportions of infants having epileptic seizures at the 18-month assessment (p=0·023; appendix). This association was most marked in those children judged to be at high risk of developmental impairment at randomisation (appendix).

Treatment modality was not significantly associated with epilepsy outcome at 18 months. Seizures were seen in 54 (30·0%) of 180 infants who received combination therapy and in 52 (29·2%) of 178 who received hormonal therapy alone (difference 0·8% [95% CI –8·8 to 10·4], p=0·90).

The associations between explanatory variables and epilepsy outcome are summarised in the appendix. The absence of any treatment effect remained in a sensitivity analysis, with logistic regression, taking into account the design factors of the study and the other variables strongly related to the outcome on univariable analyses (ie, early clinical response and lead-time to treatment; table 3). However, early clinical response remained a strong predictor of overall epilepsy outcome in this model.

Infantile spasms remained at 18 months in 55 (15·4%) of 358 infants. Spasms were seen in 16 (7%) of 229 infants who had achieved the early primary clinical response and in 39 (30·2%) of 129 who had not responded (difference 23·2% [95% CI 15·2–31·2]; p<0·001). Spasms were seen in 41 (21%) of 195 infants who were at high risk of developmental impairment at randomisation and in 14 (8·6%) of 163 infants who were at low risk (difference 12·4% [95% CI 4·8–20·0]; p=0·001). Spasms were seen in 37 (18%) of 206 children with a proven cause and in 18 (11·8%) of 152 who had no cause identified (difference 6·2% [95% CI –1·5 to 13·9]; p=0·11).

Increasing lead-time to treatment was associated with increased likelihood of having infantile spasms at the 18-month assessment (p=0·0007; appendix).

Treatment modality was not associated with epileptic spasm outcome at 18 months. Spasms were seen in 27 (15·0%) of 180 infants who received combination therapy and in 28 (15·7%) of 178 who received hormonal therapy alone (difference 0·7% [95% CI –6·9 to 8·3]; p=0·85).

	Infants with epileptic seizures at 18 months	Adjusted odds ratio (95% CI)	p value
Treatment modality			
Combination	54/178	1·4 (0·8–2·3)	0·23
Hormonal	51/177	..	..
Early clinical response			
Responder	39/228	0·2 (0·1–0·4)	<0·001
Non-responder	66/127	..	..
Developmental impairment			
High risk	71/193	1·5 (0·9–2·6)	0·12
Low risk	34/162	..	..
Hormone type			
Prednisolone	80/251	0·8 (0·4–1·4)	0·37
Tetracosactide	25/104	..	..
Hormone randomised			
Yes	37/131	1·1 (0·6–1·8)	0·84
No	68/224	..	..
Lead-time			
<7 days	27/103	ref	..
8–14 days	17/66	0·9 (0·4–1·9)	0·80
15–28 days	18/77	0·8 (0·4–1·7)	0·64
2 days to 2 months	20/58	1·3 (0·6–2·8)	0·52
>2 months	23/51	1·5 (0·7–3·3)	0·30

Data are n/N unless otherwise stated. *Lead-time to treatment not recorded in three infants and epilepsy outcome not recorded in four infants.

Table 3: **Multivariable logistic regression of epilepsy outcome (all seizure types) at 18 months***

The associations between explanatory variables and spasm outcome are summarised in the appendix. The absence of treatment effect remained in the sensitivity analysis, taking into account the design factors of the study and the other variables strongly related to the outcome in univariable analyses (ie, early clinical response and lead-time to treatment; appendix). In the multivariable analysis the absence of an early clinical response and a lead-time of more than 2 months significantly increased the odds of spasms being present at 18 months.

158 (44·1%) of 358 infants were on some form of anti-epileptic treatment at the 18-month assessment, of whom nine (2·5%) were on a ketogenic diet. Anti-epileptic treatment was being used in 69 (30·1%) of 229 infants who had achieved an early clinical response compared with 89 (69%) of 129 who had not responded (difference 38·9% [95% CI 28·0 to 49·9], p<0·001). Anti-epileptic treatment was being used in 108 (55·4%) of 195 children judged to be at high risk of developmental impairment at randomisation and in 50 (30·7%) of 163 thought to be at lower risk (difference 24·7% [95% CI 14·3 to 35·1], p<0·001). The treatment was being used in 110 (53·4%) of 206 infants with a proven cause and in 48 (31·6%) of

152 with no cause identified (difference 21·8% [95% CI 10·3–33·3], p<0·001).

Increasing lead-time to treatment was associated with a greater likelihood of being on anti-epileptic treatment at the 18-month assessment (p=0·0073; appendix).

Treatment modality was not associated with the likelihood of being on anti-epileptic treatment at the 18-month assessment. 82 (45·6%) of 180 infants initially given combination therapy and 76 (42·7%) of 178 infants given hormonal therapy alone were on anti-epileptic treatment at the 18-month assessment (difference 2·9% [95% CI –7·5 to 13·3], p=0·59).

The associations between explanatory variables and epilepsy treatment outcome are shown in the appendix. The absence of treatment effect remained in the sensitivity analysis, taking into account the design factors of the study and the other variables strongly related to outcome in univariate analyses (ie, early clinical response and lead-time to treatment; appendix). In the multivariable analysis, a high risk of developmental impairment and the absence of an early clinical response to treatment significantly increased the odds of being on anti-epileptic treatment at 18 months.

Discussion

Although the absence of spasms between days 14 and 42 of treatment was more common in infants treated with combination therapy than in those treated with hormonal therapies alone, the proportions of infants with continuing spasms, current epileptic seizures of all types, and receiving anti-epileptic treatments were similar in both treatment groups at the 18-month assessment. Similarly, developmental outcomes, as measured by VABS scores, did not differ significantly between the two treatment groups.

Our findings confirm the previously described association between early clinical response and better longer-term epilepsy prognosis: only 17% of infants who achieved early spasm cessation had a continuing epilepsy at 18 months compared with 53% of those who did not achieve an early clinical response. Early clinical responders also had significantly better developmental outcomes at 18 months than did non-responders, with a difference in mean scores of 16 points.[7,9] These results suggest that early and effective treatment is important in improving the prognosis of these infants. Some might argue that these differences have little to do with therapeutic seizure control and more to do with the degree of underlying brain disease that predisposes to both early and late seizures and developmental outcomes. However, equal numbers of children with severe underlying disease were randomised to each treatment group and a marked improvement was seen in early seizure control in one treatment group versus the other.

There is, however, an apparent paradox in these results. Early seizure control is important for longer-term epilepsy and developmental outcome but the treatment modality associated with improved early seizure control does not appear to be associated with improved longer-term outcomes. One possible explanation is that those infants who did not achieve an early response on hormonal therapy effectively received combination therapy because the majority would swiftly have been placed on vigabatrin therapy in addition to their hormonal therapy, thus diluting any comparison between the two treatment modalities. We know that 83 infants who were allocated hormonal therapy alone did not show an early clinical response and that in 61 (74%) cases their clinicians had given them vigabatrin by the end of the third month of the trial. We do not know what other anti-epileptic treatments these infants might have been exposed to or how many other infants were subsequently exposed to vigabatrin after the end of the third month.

Another possible explanation is that combination therapy was successful in abolishing spasms in a cohort of children with more severe problems and these children would not have normally responded to monotherapy with hormonal treatment. This group of responders with more severe underlying disease might be expected to have an intrinsically worse developmental outcome, thus diluting any effect of better treatment for the group as a whole. This hypothesis would imply that, within the groups of proven and no identified cause, there are subgroups of infants with better and worse developmental prognosis, something we know to be true of the proven cause group only.

The data are also compatible with the hypothesis that vigabatrin could have a negative impact on developmental outcomes. Any improvement in development that might be expected because combination therapy is more effective at achieving early spasm cessation could be undermined by a negative impact of vigabatrin on development. Vigabatrin is not known to cause neuro-developmental harm in humans but its potent GABAergic mechanism of action and recognised clinical association with drowsiness provide a biologically plausible basis for such a hypothesis, which would be compatible with the results of the previous UKISS trial.[7] However, such a hypothesis is likely to be unattractive to those who have seen vigabatrin apparently effectively control epileptic seizures and also be associated with improved developmental outcomes.[10]

Vigabatrin has also been associated with retinal toxicity and development of visual field defects. It is not possible to test visual fields accurately in children at 18 months, many of whom will have had developmental impairment, and therefore we do not know if any of our infants had developed visual field defects. The duration of vigabatrin therapy in this trial, as dictated by the trial protocol, was only 4 months. Vigabatrin-associated visual field defects appear to be associated with more prolonged therapy and therefore the risk to infants in this trial was probably very low.[11,12] However, if these defects did occur, they could have compounded any possible developmental impairment.

The trial protocol did not mandate regular video-EEG after the intial treatment period but left this to the discretion of treating clinicians. Subtle recurrence of spasms without major motor components could have been missed if video-EEG was not done. However, we feel it is unlikely that this recurrence would occur differentially in one treatment group rather than the other. Gaily and colleagues[13] have previously reported that, in a small number of children treated with vigabatrin, the spasms modify into a subtle variant within 2 weeks of treatment and it is possible that these spasms might be missed clinically. It could be argued that if this effect was occurring in children treated with combination therapy in our study and not in the group receiving hormonal therapy only, then a population of patients with subtle undiagnosed relapses in the combination group possibly went untreated, which might have an impact on the longer-term developmental outcome at 18 months. However, the study by Gaily and colleagues did not comment on whether the same effect occurs when hormonal therapy is used, as only one of 44 patients in the study was given any form of hormonal treatment as first-line therapy.

There is much debate about whether one form of hormonal treatment is better than the other, and in the UKISS trial we found no difference between prednisolone and tetracosactide depot with respect to either epilepsy or developmental outcomes.[7,14] Both hormonal treatments were incorporated in the ICISS trial and we allowed parents to choose the type of hormonal therapy their child received if they did not wish for the type of hormonal therapy to be randomised. Clinicians were not allowed to choose the type of hormonal therapy on an individual basis but a participating centre could choose a type of hormonal therapy provided all patients at their centre received the same choice. Therefore, as hormonal therapy was not randomised in many cases, drawing conclusions in this respect is very difficult. However, accepting these caveats, the early clinical response observed in the ICISS trial suggests that prednisolone was associated with reduced likelihood of achieving an early electroclinical response than tetracosactide depot.[6] However, data at the 18-month follow-up do not suggest that any one form of hormonal therapy was associated with better developmental or epilepsy outcomes.

Unsurprisingly, infants at high risk of developmental impairment at randomisation did worse than those deemed to be at lower risk. Mean VABS scores for the high-risk group were 20 points lower than those for the low-risk group and high-risk infants were significantly more likely to have continuing epileptic seizures, and spasms in particular, at 18 months than were low-risk infants. This outcome is likely to be because the high-risk group almost invariably had another reason, apart from their spasms, to have poor developmental and epilepsy outcomes.

High risk of developmental impairment was strongly associated with the post-hoc determined variable of proven cause ($p<0·001$), and in the majority of these infants an underlying cause was found. In the UKISS trial, we found that the treatment modality that was more successful at early eradication of spasms was associated with a better developmental outcome in infants with no proven cause, but this was not the case at the 18-month assessment in ICISS.[7] VABS might not be a sufficiently sensitive instrument to detect subtle differences in adaptive behaviour at 18 months. Moreover, 18 months of age is possibly too early to see a difference between the two treatment groups. For this reason, we intend to assess developmental attainment at 42 months (3·5 years) of age.

Although the two variables—risk of developmental impairment and proven cause—were associated, both contributed independently to explaining the variance in developmental scores. Presumably, this finding reflects the underlying causes that affect later development but were not evident at the time of randomisation.

The finding that longer lead-time to treatment was associated with worse developmental outcome is compatible with the hypothesis that infantile spasms cause neurological damage and that the longer they persist the more likely they are to lead to developmental impairment. This association between lead-time and developmental impairment persisted in our study when controlling for early clinical response, risk of developmental impairment, underlying cause, age at diagnosis, ongoing epilepsy at 18 months, and treatment modality. This result is consistent with our findings from the UKISS trial and underlines the importance of diagnosing and rapidly treating these children at the earliest opportunity.

Continuing epilepsy at 18 months was a strong predictor of developmental outcome even when controlling for initial response to therapy, lead-time to treatment, risk of developmental impairment, and underlying cause (table 2). One explanation for this finding might be that persistent epilepsy at 18 months is a marker for more prolonged exposure to epileptic encephalopathy in infancy and therefore explains why these children score less well on the VABS assessment. Persistent epilepsy at 18 months might result in greater exposure to anti-epileptic medications, which might also have a negative impact on development. Although most children who had seizures at 18 months were not having spasms, continuing seizure activity was possibly affecting development.

The association between risk of developmental impairment and lead-time to treatment (appendix) is also important. This result showed that children judged to be at high risk of developmental impairment at randomisation had a longer lead-time to treatment. Diagnostic overshadowing by the underlying condition (particulalrly when the cause is established) might make recognition of infantile spasms more difficult. Moreover, children who already show signs of neurological impairment might not be treated as rapidly as other children because either their parents or clinicians respond less rapidly to a

new problem in a child who is already displaying multiple problems.

Longer lead-time to treatment was also associated with worse epilepsy outcomes. In particular, a lead-time of more than 2 months significantly increased the odds of having epileptic spasms at 18 months even when controlling for all other important explanatory variables and the design factors of the study (appendix). This is an important finding since it implies that earlier treatment will reduce the later burden of epilepsy. This finding is consistent with the previously described observation that a treatment lag of more than 2 months in children with Down's syndrome and infantile spasms is associated with worse epilepsy outcomes.[15] This finding might be compatible with the idea that repeated uncontrolled epileptic seizures over a long duration in early life might set up epileptic circuits within the brain that are then difficult to control in later life with current anti-epileptic treatments. Early effective treatment for infantile spasms might not only be anti-ictal but also anti-epileptogenic.

The finding that increasing age at randomisation was related to a poorer developmental outcome in this dataset was surprising, as previous studies have indicated that younger children were at greater risk of developmental impairment associated with epileptic encephalopathy than were older children.[16] However, this finding was confounded by the risk of developmental impairment and lead-time to treatment: children who were older at randomisation were also more likely to have a higher risk of developmental impairment at randomisation and a longer lead-time to treatment, both of which independently predicted a poorer developmental outcome. Therefore, we do not think it is possible to acertain from these data whether age at randomisation, and, by implication, age at onset of spasms is an important factor influencing developmental outcome from epileptic spasms.

ICISS is, to our knowledge, the largest study or clinical trial of infantile spasms ever completed. Key strengths of the trial are that it was adequately powered both for its primary clinical outcome (cessation of spasms between days 14 and 42 of treatment) and its developmental outcome, and that we managed to follow up 362 of 370 infants who were still alive at 18 months. Loss to follow-up of only 15 children at 18 months from an original cohort of 377 patients with infantile spasms is remarkable, given the severity of the epilepsy syndrome and the geographical spread of the cohort. Five patients were lost to follow-up from the combination group and ten from the hormonal therapy alone group (figure 2). We do not think that the small attrition in this cohort is likely to have introduced any biases that could undermine the results presented. Although parents and treating clinicians were not masked to treatment allocation, assessors of developmental and epilepsy outcomes at 18 months were masked to treatment allocation. We relied on a structured epilepsy questionnaire to assess the epilepsy outcomes at 18 months; this approach has its limitations when compared with video EEG telemetry. Epilepsy questionnaires were the most feasible method to use in our trial, which covered five countries and had 377 participants. We used the VABS as our measure of development. This scale was a pragmatic instrument to use as it can be administered via telephone interview and has been validated in multiple countries. The scale does not give a global or comprehensive assessment of development but assesses one aspect of development—namely, adaptive behaviour—in several domains. However, a strong correlation exists between VABS composite scores and developmental quotients derived from more comprehensive developmental instruments such as the Bayley Scales of Infant and Toddler Development.[17,18]

In conclusion, this study has shown that early clinical response to treatment is a strong predictor of both developmental and epilepsy outcomes at 18 months. Our findings also show that longer lead-time to treatment is associated with poorer outcomes. The obvious implication for clinicians is that rapid diagnosis and effective treatment of infantile spasms is essential to improve outcomes. The finding that the treatment that was associated with a better early clinical response (ie, combination therapy) is not necessarily associated with a better developmental and epilepsy outcome at 18 months is surprising but could be explained by the fact that many children who did not respond to hormonal monotherapy would have rapidly received additional vigabatrin and therefore would have effectively received combination therapy as well. Assessment at 18 months is possibly also too early to discern more subtle differences in developmental outcome, given the instrument we were using; longer-term follow-up of these children at 42 months is needed to discern treatment effects.

Contributors

FJKO'C, SWE, EH, ALJ, CRK, ALL, RWN, CMV, and JPO were involved in all stages, from protocol design to completion of the manuscript, had access to the data, and had final responsibility for the decision to submit for publication. MTM, MN, DR, and BS were involved in all stages after protocol design as national co-collaborators and had a major role in obtaining relevant approvals in their countries. FDA and AAM were involved in keeping track of infants and their parents from follow-up onwards. RP, MCB, and ML were involved in data analysis and thereafter. SWE also built the trial website and managed the trial office. JPO also reviewed all case report forms for data accuracy. ALJ, MCB, and FJKO'C also did the statistical analysis of the trial results. JPO was Chief Investigator until November, 2011, when FJKO'C took over. FJKO'C, SWE, and JPO are the guarantors of the data.

Declaration of interests

FJKO'C, SWE, EH, ALL, and JPO have received a payment from Marathon Pharmaceuticals for intellectual property during the course of this study. The study sponsor has received a payment from UCB Biopharma for intellectual property during the course of this study. DR has received a grant from the charity BRONNER-BENDER Stiftung during the course of the study. FDA, MCB, ALJ, CRK, ML, MTM, AAM, RWN, MN, RP, BS, and CMV declare no competing interests.

Data sharing

No additional data are available for this Article.

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