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

Title as submitted: The International Collaborative Infantile Spasms Study (ICISS) comparing hormonal treatment (prednisolone or tetracosactide depot) alone to hormonal treatment with vigabatrin: a multi-centre randomized controlled trial. Developmental and epilepsy outcomes at 18 months of age.

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Summary

Background: Infantile spasms constitute a severe epileptic encephalopathy. We have previously shown that combining vigabatrin with hormonal therapy was more effective than hormonal therapy alone at stopping spasms between days 14 and 42 of treatment. We aimed to assess whether combination therapy was associated with better developmental and epilepsy outcomes at 18 months of age.

Methods: In this multicentre, open-label randomised trial, 102 hospitals (Australia [three], Germany [11], New Zealand [two], Switzerland [three], and the UK [83]) enrolled infants who had a clinical diagnosis of infantile spasms and a hypsarrhythmic (or similar) 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 prednisolone 10 mg four times a day or intramuscular tetracosactide depot 0.5 mg (40 IU) on alternate days with or without vigabatrin 100 mg/kg per day. The main outcomes at 18 months were neurodevelopment as assessed by Vineland Adaptive Behaviour Score and the presence of epileptic seizures in the previous month as recorded by parents and carers. Analysis was by intention to treat. The trial is registered with The International Standard Randomised Controlled Trial Number (ISRCTN), number 54363174, and the European Union Drug Regulating Authorities Clinical Trials (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 (186) or hormonal therapy alone (191). 362 infants were assessed for developmental and epilepsy outcomes at 18 months, 181 in each treatment group. Mean (SE) VABS score did not differ significantly between treatment groups (73.9 (1.3) versus 72.7 (1.4), difference -1.2 (95%CI -4.9 to 2.6), *t*=0.6, *df*=360 *p*=0.55). Presence of epilepsy at the assessment at 18 months of age was similar in both treatment groups (30% versus 29.2%, difference 0.8%, 95%CI –8.8% to 10.4%, χ^2 = 0.03 (1df), *p* = 0.9). Presence of spasms was also similar in both treatment groups (15% versus 15.7%, difference 0.7%, 95%CI -6.9% to 8.3%; χ^2 = 0.04 (1 df), *p*=0.85) . Initial control of spasms between day 14 and 42 of treatment was associated with higher VABS scores at 18 months (79.1 (1.2) versus 63.2 (1.1), difference 15.9 (95%CI 12.4 to 19.5), *t*=8.8, *df*=360 *p*<0.001) and with higher chance of absence of seizures at 18 months (17% versus 51.9%, difference 34.9%, 95%CI 24.8% to 45.0%; χ^2 = 48·2 (1 df), *p*<0·001). Increasing lead-time to treatment was associated with lower VABS scores (coefficient = - 3.3 (SE 0.7) *t*= -4.97, *df*=358 *p* = 0.0001) and worse epilepsy outcomes (χ^2 for linear trend =5.2, p=0.023).

Interpretation:

Although combination therapy was associated with better early clinical response it was not related to 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. The implication for clinicians is that rapid diagnosis and effective treatment of IS may improve outcomes.

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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 2]. They were the first described epileptic encephalopathy – a condition in which the epileptic activity itself contributes to cognitive and neurological decline[3]. They are also the most prevalent epileptic encephalopathy affecting approximately 1 in 2500 infants[4]. The implication of the epileptic encephalopathy concept is that effective treatment that shortens the duration of the encephalopathy will lead to better developmental and epilepsy outcomes.

We have previously shown in the ICISS trial 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 day 14 and 42 of treatment inclusive) and achieving an electroclinical response [5]. 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, we thought this effect would be most clearly seen in those children who had no obvious underlying aetiology for their infantile spasms since these children have no known reason for poor development other than their spasms[6]. In this paper we report the developmental and epilepsy outcomes of the ICISS trial infants as they reached 18 months of age.

Methods

Study design

ICISS was a pragmatic multicentre parallel group open-label trial with some blind outcome measures. 102 hospitals enrolled patients (Australia 3, Germany 11, New Zealand 2, Switzerland 3 and UK 83). Local investigators enrolled and managed patients and collected information related to cessation of spasms. Treatment allocation was undertaken 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 protocol is available at www.iciss.org.uk.

Participants

Inclusion criteria were a clinical diagnosis of infantile spasms by the local investigator and an EEG that was judged by local neurophysiologists to be hypsarrhythmic or similar, compatible with the diagnosis of infantile spasms. Exclusion criteria were: age under 2 months or over 14 months, a delay > 7 days since the diagnosis, a diagnosis of tuberous sclerosis, previous treatment for infantile spasms or previous use of hormonal treatments or vigabatrin, the coincidence of another condition likely to be lethal before outcome assessment, predictable lack of availability for follow up to 18 months, 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 the parents or guardian.

Randomisation and masking

Patients were randomized centrally using an interactive computer system accessed independently by recruiting clinicians via the trial website. Patients were allocated to receive combination therapy or hormonal therapy alone in a 1:1 ratio. Where parents consented, there was an additional randomization of type of hormonal therapy used, prednisolone or tetracosactide depot, in a 1:1 ratio. Block randomisation (random block size of less than 10) was used and investigators were blind to actual block size. Randomization 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.

Aetiology was determined by FJKO'C and JPO who were blind to treatment allocation, using information available from clinical history, examination and investigations. The aetiology was classified as proven, no aetiology identified or 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, in the UK), tetracosactide depot (Synacthen Depot, Alliance Pharmaceuticals, Chippenham, in the UK), and vigabatrin (Sabril, Aventis Pharma, West Malling, in the UK). The same products were used outside the UK and, although the market authorization holder varied, this did not affect the dose and drugs used. Prednisolone was given orally (10 mg four times a day) for two 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 two 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 continued at the same dose on a body weight 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 that was considered to be in the infant's best interest, and in non-responders. Drug accountability was monitored by direct questioning.

Parents filled in a daily record of spasm frequency for the first 42 days of the trial and there was a mandated minimum schedule of out-patient 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 aetiologies. A structured paediatric epilepsy history was taken at 18 months of age by assessors who were blinded to initial treatment allocation (AM in UK, Australia and New Zealand. 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 and/or the ketogenic diet. 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 and was categorized into five time periods (7 days or less, 8 to 14 days, 15 to 28 days, 29 days to 2 months and greater than 2 months) or as not known. Clinical onset of spasms precedes (often by days or weeks) the formal diagnosis of IS, which requires physician assessment and EEG confirmation (see Figure 1).

Development was assessed by an assessor (AM in UK, Australia and New Zealand. FDA in Germany and Switzerland) who were blind to treatment allocation, by means of telephone interview at 18 months of age with the Vineland Adaptive Behaviour Scales (VABS). These scales assess 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 this yields a mean score of 100 with a standard deviation of 15.

Pharmacovigilance

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 serious if it was life-threatening, caused death, resulted in persistent or significant disability or required hospitalization. Causality was determined 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 the treatment of fever. Central monitoring of data was undertaken by JPO, FOC, & SE who reviewed the case report forms as they were returned to the trial centre in Bath.

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.

Statistical Analysis

The target number for patients included in the trial had been determined by the power calculation undertaken to see a difference in both the early primary outcome (i.e. cessation of spasms) and the late primary outcome (i.e. development at 18 months). The data from our previous clinical trial (UKISS) had shown that a difference in development between the two treatment arms was only found in the sub-group with no identified aetiology[6]. In this group, the VABS score was 88 for those on hormonal treatments alone and we judged that this would need to improve by approximately half a standard deviation (i.e. 7 points) on combination therapy to be considered clinically meaningful. Consequently the number of participants required to see an improvement in mean VABS score from 88 to 95 in the sub-group with no identified aetiology, using 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 exceeding the requirements for 80% power for the early primary outcome (i.e. cessation of spasms between day 14 and 42 of treatment) and the late outcome of development. 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 performed under the intention-to-treat principle. The primary explanatory variable of interest was the effect of treatment modality. In addition, we anticipated that initial response to treatment (i.e. absence of spasms between Day 14 and Day 42), lead-time to treatment of spasms, presence of an underlying aetiology 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 may also explain some of the variation in developmental scores. Differences in Vineland composite scores were initially compared using two-sample t-tests for categorical variables and either ANOVA or linear regression for continuous explanatory variables. We tested the assumptions of normality and homogeneity

of variances using Shapiro-Wilk's and Bartlett's tests, respectively. Multivariable analyses controlling for the design factors of the study (i.e. 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 undertaken fitting multivariable linear regression models. Models' goodness-of-fit were compared using the Bayesian Information Criterion.

For the secondary outcomes at age 18 months (i.e. 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 using Pearson's χ^2 tests. Results are summarised as treatment differences and 95% confidence intervals (CI). Sensitivity analyses controlling for the design factors of the study and other variables significantly associated with the secondary outcomes were performed fitting logistic regression models. These models were not over-fitted[7]. Statistical analyses were performed using Stata IC 11·2 (Statacorp, College Station, Texas, USA) and R version 3.4.2 (The R Foundation for statistical computing, Vienna, Austria).

The trial is registered with The International Standard Randomised Controlled Trial Number (ISRCTN), number 54363174, and the European Union Drug Regulating Authorities Clinical Trials (EUDRACT) number 2006-000788-27.

Role of 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. The senior authors (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

From the original cohort, 362 (96%) of 377 underwent developmental assessment with the Vineland Adaptive Behaviour Scales (see Figure 2). There were no clinically important imbalances between treatment groups

with regard to baseline characteristics (see Table A appendix). 299 (83%) of the remaining cohort underwent assessment in their 18th month, and 352 had been assessed by the end of their 19th month (97%). Ten infants were assessed after the 19th month: 5 at 20 months, 2 at 22 months, 1 at 23 months, 1 at 25 months and 1 at 32 months. A total of 181 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. The acute cause of death in the seven children 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 aetiology was proven in 209 (58%) cases and no aetiology was identified in 153 (42%) cases of the cohort that was followed up at 18 months.

Data on epilepsy outcome was available on 358 (95%) of the original cohort of 377. Two children who had developmental assessments did not provide epilepsy histories at 18 months, and in the cases of two children it was uncertain from history and the epilepsy questionnaire whether epileptic seizures were present.

Developmental outcome:

Vineland composite scores in the cohort ranged from 44 to 138 (mean 73.3, standard deviation 18.2). Mean composite scores (SE) were higher in those infants judged to be at low risk of developmental impairment at randomisation compared to those at high risk (84.6 (1.3) versus 63.9 (0.91), difference 20.7 (95% CI 17.6 to 23.8), t = 13.1, p < 0.001). Composite scores were also higher in those infants who had achieved a primary clinical response (i.e. cessation of spasms between day 14 to 42 inclusive) than in those who had not (79.1 (1.2) versus 63.2 (1.1), difference 15.9 (95%CI 12.4 to 19.5), t=8.8, p<0.001). Increasing lead-time to treatment was related to mean composite scores with each increase in lead-time category being associated with a drop in composite score (see Table 1 and Figure 3). Increasing lead-time to treatment was also

associated with the risk of developmental impairment with those children at high risk of impairment at ransomisation having longer lead-times to treatment (see Web Appendix Table B)

The presence of an underlying aetiology was associated with a lower VABS composite score than in those with no identified aetiology (66.8 (1.0) versus 82.5 (1.5), difference 15.7 (95% CI 12.2 to 19.2), t=8.9, p<0.001). The presence of current epileptic seizures at 18 months was also associated with lower VABS composite scores (60.5 (1.1) versus 79.0 (1.1), difference 18.5 (95% CI 14.8 to 22.2), t=9.8, p<0.001).

Vineland scores were also related to age (in days) at randomisation (coefficient -0.06 (SE 0.013) t=-4.2 p<0.001) with each one day increase in age at randomisation being associated with a drop of 0.06 points on the Vineland scale. Age at randomisation is associated with the risk of developmental impairment assessed at time of inclusion into the trial. The mean age at randomisation (SE) in the high-risk group was 233 days (5.6) versus 197 days (4.6) in the low risk group (mean difference 35.9, (95% CI 50.4 to 21.3) t = 4.9, 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) t=6.5, p <0.001) .The association between Vineland score and age at randomisation disappears completely when controlling for risk of developmental impairment and lead-time to treatment.

There were no significant differences in VABS mean composite scores between the combination therapy group and the hormonal therapy alone group (73.9 (1.3) versus 72.7 (1.4), difference -1.2 (95%CI -4.9 to 2.6), t=0.6, p=0.55). Stratifying the data by risk of developmental impairment, there were still no significant differences in VABS scores between the treatment groups. In those children at high risk of developmental impairment at randomisation, the mean composite scores in the combination therapy group were (63.6 (1.2)) compared to those in the hormonal therapy alone group (64.1 (1.4), difference 0.5 (95%CI -3.1 to 4.1) t=0.26, p=0.79). In those children at lower risk for developmental impairment the mean scores in the combination

therapy group were (86.5 (1.8)) and in the hormonal therapy alone group were (82.7 (2.0), difference -3.8 (95% CI -9 to 1.5), *t*=1.4, *p*=0.15). Similarly there was no interaction between treatment modality and aetiology with respect to VABS composite scores. The mean VABS scores in the no aetiology identified group for those on combination therapy was 83.5 (2.1) compared to 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 Vineland scores are summarised in Web Appendix Table C.

The lack of any treatment effect on VABS scores remained in a sensitivity analysis, using multiple linear regression, taking into account the design factors of the study (i.e. controlling for risk of developmental impairment, type of hormone treatment, and whether or not hormonal treatment was randomized) and the other explanatory variables strongly associated with the outcome (i.e. early clinical response, lead-time to treatment, presence of an underlying aetiology, and continuing epilepsy at 18 months) (see Table 2). In the multivariable analysis, risk of developmental impairment, early clinical response, lead-time to treatment , presence of an underlying aetiology, and continuing epilepsy at 18 months remained significant independent predictors of developmental outcome.

Epilepsy outcomes:

(i) Epileptic seizures at 18 month assessment

The presence of epileptic seizures of any type at 18 months was seen in 106 of 358 (30%) infants. Seizures were seen in 39 of 229 (17%) who had achieved a primary early clinical response and in 67 of 129 (51.9%) of those who had not achieved spasm cessation (difference 34.9%, 95%CI 24.8% to 45.0%; χ^2 = 48·2 (1 df), *p*<0·001).

Epileptic seizures were seen in 72 of 195 (36.9%) of infants who were at high risk of developmental impairment at randomisation and in 34 of 163 (20.9%) of those at low risk (difference 16%, 95%CI 6.4% to

25.6%; χ^2 = 10.9 (1 df), *p*=0·001). Similarly seizures were seen in 72 of 206 (35%) infants who had a proven aetiology and 34 of 152 (22.4%) of those with no aetiology identified (difference 12.6%, 95%CI 2.8% to 24.4%; χ^2 = 6.7 (1 df), *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 (χ^2 for linear trend =5.2,(1 df) *p*=0.023 see Web Appendix Table D). This association was most marked in thoe children judged to be at high risk of developmental impairment at randomisation (see Web Appendix Tables E and F)

Treatment modality was not significantly associated with epilepsy outcome at 18 months. Seizures were seen in 54 of 180 (30%) infants who received combination therapy and in 52 of 178 (29.2%) who received hormonal therapy alone (difference 0.8%, 95%CI -8.8% to 10.4%; χ^2 = 0.03 (1 df), *p*=0.9).

The associations between explanatory variables and epilepsy outcome are summarised in Web Appendix Table G. The lack of any treatment effect remained In a sensitivity analysis, using logistic regression, taking into account the design factors of the study and the other variables strongly related to outcome on univariable analyses (i.e. early clinical response and lead-time to treatment)(see Table 3). However, early clinical response remained a strong predictor of overall epilepsy outcome in this model.

(ii) Infantile Spasms

Infantile spasms remained at 18 months in 55 of 358 (15.4%) infants. Spasms were seen in 16 of 229 (7%) infants who had achieved the early primary clinical response and in 39 of 129 (30.2%) who had not responded (difference 23.2%, 95%CI 15.2% to 31.2%; χ^2 = 34.3 (1 df), *p*<0.001). Spasms were seen in 41 of 195 (21%) infants who were at high risk of developmental impairment at randomisation and in 14 of 163 (8.6%) of infants who were at low risk (difference 12.4%, 95%CI 4.8% to 20.0%; χ^2 = 10.6 (1 df), *p*=0.001). They were seen in 37 of 206 (18%) children with a proven aetiology and in 18 of 152 (11.8%) who had no aetiology identified (difference 6.2%, 95%CI – 1.5% to + 13.9%; χ^2 = 2.5 (1 df), *p*=0·11).

Increasing lead-time to treatment was associated with increased likelihood of having infantile spasms at the 18-month assessment (χ^2 for linear trend =11.6, *p*=0.0007 see Web Appendix Table D)

Treatment modality was not associated with epileptic spasm outcome at 18 months. Spasms were seen in 27 of 180 (15%) who received combination therapy and in 28 of 178 (15.7%) who received hormonal therapy alone (difference 0.7%, 95%CI -6.9% to 8.3%; χ^2 = 0.04 (1 df), *p*=0.85).

The associations between explanatory variables and spasm outcome are summarised in Web Appendix Table H. The lack 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 on univariable analyses (i.e. early clinical response and lead-time to treatment)(see Web Appendix Table J). In the multivariable analysis the lack of early clinical response and a lead-time of greater than two months significantly increased the odds of spasms being present at 18 months.

(iii) Epilepsy treatments:

158 of 358 (44.1%) infants were on some form of anti-epileptic treatment (AET) at the 18-month assessment, of whom 9 (2.5%) were on the ketogenic diet. AET was being used in 69 of the 229 (30.1%) who had achieved an early clinical response compared with 89 of 129 (69%) who had not responded (difference 38.9%, 95%CI 28.0% to 49.9% χ^2 =50.5 (1df), *p*<0.001). AET was being used in 108 of 195 (55.4%) of those children judged to be at high risk of developmental impairment at randomisation and in 50 of 163 (30.7%) of those thought to be at lower risk (difference 24.7%, 95%CI 14.3 to 35.1, χ^2 = 21.98 (1df), *p* < 0.001). It was being used in 110 of 206 (53.4%) of those with a proven aetiology and in 48 of 152 (31.6%) of those with no aetiology identified (difference 21.8%, 95%CI 10.3% to 33.3%; χ^2 = 16.9 (1 df), *p*<0·001).

Increasing lead-time to treatment was associated with a greater likelihood of being on AET at 18-month assessment (χ^2 test for linear trend = 7.21 (1df), *p*=0.0073, see Web Appendix Table D)

Treatment modality was not associated with the likelihood of being on AET at the 18-month assessment. 82 of 180 (45.6%) infants initially given combination therapy and 76 of 178 (42.7%) of infants given hormonal therapy alone were on AET at the 18-month assessment (difference 2.9%, 95%CI - 7.5% to 13.3%, χ^2 = 0.30 (1df) *p*=0.59).

The associations between explanatory variables and epilepsy treatment outcome are shown in Web Appendix Table K. The lack 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 on univariate analyses (i.e. early clinical response and lead-time to treatment)(see Web Appendix Table L). In the multivariate analysis, high risk of developmental impairment and the lack of an early clinical response to treatment significantly increased the odds of being on AET at 18 months.

Discussion:

Although absence of spasms between days 14 and 42 of treatment was more common in those infants treated with combination therapy than with hormonal therapies alone, the proportion of infants with continuing spasms, current epileptic seizures of all types, and receiving anti-epileptic treatments was similar in both treatment groups at the 18 month assessment. Similarly there was no difference in developmental outcome, as measured by Vineland Adaptive Behaviour Scores, between the two treatment groups.

Our findings confirm the previously described relationship between early clinical response and better longer-term epilepsy prognosis: only 17% of those who achieved early spasm cessation had a continuing epilepsy at 18 months compared to 53% of those who had failed to achieve an early clinical response. The early clinical responders also had significantly better developmental outcomes at 18 months than the non-responders, with a difference in mean scores of 16 points[6 8]. These results suggest that early 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 seizure and developmental outcomes. However, equal numbers of

children with severe underlying disease will have been randomised to each treatment arm and there was clearly a marked improvement in early seizure control in one treatment arm 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 it appears that the treatment modality associated with better early seizure control is not associated with better longer-term outcomes. One possible explanation is that those infants who failed to achieve an early response on hormonal therapy, effectively received combination therapy because the majority of them will 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 children who were allocated hormonal therapy alone did not show an early clinical response and that in 61 cases (74%) their clinicians had given them vigabatrin by the end of month 3 of the trial. We do not know what other AEDs they may have been exposed to or how many other children were subsequently exposed to vigabatrin after the end of month 3.

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 aetiology there are subgroups of infants with better and worse developmental prognosis, something we know to be true of the proven aetiology 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 neurodevelopmental 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 and it would be compatible with the results of the previous UKISS trial[6]. However, such a hypothesis is likely to be unattractive to many who have seen vigabatrin apparently effectively control epileptic seizures in other studies and also be associated with improved developmental outcomes[9].

Vigabatrin has also been associated with retinal toxicity and the development of visual field defects. It is not possible to test visual fields accurately in children at 18 months, many of whom will have been developmentally impaired and therefore we do not know if any of our infants had developed visual field defects. The duration of vigabatrin therapy in this trial 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[10 11]. However, if they did occur it is feasible 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. It is possible that subtle recurrence of spasms without major motor components could be missed if video-EEG was not performed. However, we feel it is unlikely that this would occur differentially in one treatment arm rather than the other. It has been previously reported by Gaily et al. that in a small number of children treated with vigabatrin, the spasms modify into a subtle variant within two weeks of treatment and it is possible that these might be missed clinically[12]. It could be argued that if this phenomena was occurring in the children treated with combination therapy in our study and not in the hormonal therapy only arm, then this may mean that there is a population of patients with subtle undiagnosed relapses in the combination arm that went untreated and that this may impact on the longer term developmental outcome at 18 months. However, the Gaily study could not comment on whether the

same phenomenon occurs when hormonal therapy is used as only one out 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 United Kingdom Infantile Spasm Study (UKISS) we found no difference between the two with respect to either epilepsy or developmental outcomes[6 13]. Both hormonal treatments were incorporated in this 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 the patients at their centre received the same choice. Therefore, as hormonal therapy was not randomised in many cases it is very difficult to draw conclusions in this respect. However, accepting these caveats, in the paper detailing the early clinical response in the ICISS trial, there is a suggestion that prednisolone was associated with less chance of achieving an early electro-clinical response than tetracosactide depot[5]. There is, however, no suggestion from the data at the 18 month follow-up that any one form of hormonal therapy was associated with either better developmental or epilepsy outcomes.

Unsurprisingly the children with high risk of developmental impairment at randomisation did worse than those deemed to be at lower risk. Their mean VABS scores were 20 points lower than the low risk group and they were significantly more likely to have continuing epileptic seizures and spasms in particular at 18 months. This 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.

The variable “high risk of developmental impairment” was strongly associated with the post-hoc determined variable of “proven aetiology” (χ^2 = 105.3 (1df), p <0.001), and in the majority of these infants an underlying

aetiology was found. In our previous trial, we had found that the more successful treatment modality at early eradication of spasms was associated with a better developmental outcome in those children with no proven aetiology but this was not the case in this trial at the 18-month assessment[6]. It may be that the VABS is not a sufficiently sensitive instrument to detect subtle differences in adaptive behaviour at 18 months. It is also possible that 18 months of age is too young to see a difference between the two treatment groups. For this reason we intend to assess developmental attainment at 3 and a half years of age.

Although the two variables, risk of developmental impairment and proven aetiology, were associated, they both contributed independently to explaining the variance in developmental scores. Presumably, this reflects the underlying aetiologies that impact on later development that 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 persists in our study when controlling for early clinical response, risk of developmental impairment, underlying aetiology, age at diagnosis, ongoing epilepsy at 18 months and treatment modality. This result is consistent with our findings in the previous UKISS study. It underlines the importance for clinicians to diagnose and rapidly treat these children at the earliest opportunity.

It is notable that continuing epilepsy at 18 months was a strong predictor of developmental outcome even when controlling for initial response to therapy, lead-time, risk of developmental impairment, and underlying aetiology (see Table 2). One explanation for this might be that persistent epilepsy at 18 months is a marker for more prolonged exposure to the epileptic encephalopathy in infancy and therefore this is why these

children score less well on the Vineland assessment. It may be that persistent epilepsy at 18 months results in greater exposure to antiepileptic medications which also have a negative impact on development. Although most of the children who had seizures at 18 months were not having spasms, it is also possible that the continuing seizure activity was affecting development.

The association between risk of developmental impairment and lead-time to treatment (see Table C) is also important. This result demonstrated 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 aetiology is established) may make recognition of infantile spasms more difficult. It may also be the case that these children who already show signs of neurological impairment are not treated as rapidly because either 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 greater than 2 months significantly increased the odds of still having epileptic spasms at 18 months even when controlling for all other important explanatory variables and the design factors of the study (see Table G). This is an important finding since it implies that earlier treatment will reduce the later burden of epilepsy. It is consistent with the previously described observation that treatment lag of greater than 2 months in the specific scenario of children with Down's syndrome and infantile spasms is associated with worse epilepsy outcome[14]. This finding may be compatible with the idea that repeated uncontrolled epileptic seizures over a long duration in early life may 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 may not only be anti-ictal but also anti-epileptogenic.

It was surprising to find that increasing age at randomisation was related to a poorer developmental outcome in this dataset as previously it has been thought that younger children were more at risk of developmental impairment associated with epileptic encephalopathy[15]. However, this finding in our data was confounded by 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 variables independently predicted a poorer developmental outcome. Therefore we do not think it is possible to say from this data whether age at randomisation, and, by implication, age at onset of spasms is an important factor influencing developmental outcome form epileptic spasms.

ICISS is the largest study or clinical trial of IS ever completed. Obvious strengths of the trial are that it was adequately powered both for its primary clinical outcome (cessation of spasms between day 14 and 42 of treatment) and its developmental outcome, and that we managed to follow up 362 of the 370 infants who were still alive at 18 months. The loss of only 15 children at 18 months from an original cohort of 377 infantile spasm patients is remarkable given the severity of the epilepsy syndrome and the geographical spread of the cohort. Five patients were lost from the combination arm and 10 from the hormonal therapy alone arm (see 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 blinded to treatment allocation, the assessors of developmental and epilepsy outcomes at 18 months were blind to treatment allocation. We relied on a structured epilepsy questionnaire to assess the epilepsy outcomes at 18 months and obviously this has limitations when compared to video EEG telemetry. Epilepsy questionnaires were the most feasible method to use in our trial that covered five countries and had 377 participants. We used the Vineland Adaptive Behaviour Scale (VABS) as our measure of development. It was a pragmatic instrument to use as it can be administered via telephone interview and it has been validated in multiple countries. It does not give a global or comprehensive assessment of development but assesses one aspect of

development, namely adaptive behaviour, in several domains. However there is a strong correlation between VABS composite scores and developmental quotients derived from more comprehensive developmental instruments such as the Bayley scales of infant and toddler development[16 17].

This study has shown that early clinical response to treatment is a strong predictor of both developmental and epilepsy outcomes at 18 months. It has also shown that longer lead-time to treatment is associated with poorer outcomes. The obvious implication for clinicians is that rapid diagnosis and effective treatment of IS is essential to improve outcomes. The finding that the treatment that was associated with a better early clinical response (i.e. combination therapy) is not associated with a better developmental and epilepsy outcome at 18 months is surprising but may be explained by the fact that many of those children who failed to respond to hormonal monotherapy will have rapidly received additional vigabatrin and therefore have effectively received combination therapy as well. It is also possible that assessment at 18 months is too early to discern more subtle differences in developmental outcome given the instrument we were using and that longer-term follow-up of these children at 42 months is needed to discern treatment effects.

Contributions:

Except where indicated, all authors were involved from protocol design to completion of the paper, had access to the data, and final responsibility for the decision to submit for publication. MM, MN, DR and BS as National Co-collaborators were involved in all stages after protocol design and had a major role in obtaining relevant approvals in their countries. FDA and AM were involved in keeping track of infants and their parents from follow up onwards. RP, MCB and ML were involved from data analysis and thereafter. SE also built the trial website and managed the trial office. JPO also reviewed all CRFs for data accuracy. ALJ, MCB and FJKO'C also performed the statistical analysis of the trial results. JPO was Chief Investigator until November 2011 when FJKO'C took over. FJKO'C, SE, and JPO are the guarantors of the data.

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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, MM, AAM, RWN, MN, RP, BS, and CMV declare no competing interests.

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Research in context:

Evidence before this study:

We have conducted a Cochrane systematic review into the treatment of infantile spasms that we have continued to update to April 2018. In identifying research in the area we search the Cochrane Epilepsy Group Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (1946 to April 2018), EMBASE (1980 to March 2003), ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform (ICTRP) and the reference lists of all retrieved articles. We have found 20 small RCTs (fewer than 100 patients enrolled) and 3 larger RCTs (more than 100 patients enrolled) that have looked at a total of 12 different pharmaceutical agents. Overall methodological quality of the studies has been poor. The most popular and commonly used treatment modalities are either hormonal treatments (prednisolone, natural or synthetic ACTH) or vigabatrin. The strongest evidence prior to 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 the long-term neurodevelopmental outcome compared with vigabatrin in infants in whom no underlying cause for their spasms could be found. It 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, suggests that 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:

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

Implications of all the available evidence:

The ICISS study suggests a modality of treatment that will stop spasms faster and in more children than has previously been achieved with existing treatment strategies. It has not demonstrated that this treatment modality is associated with better 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 spasms is important in achieving improved outcomes in these patients.

Table 1

Lead-time to treatment and Vineland Composite Scores at 18 months*

Lead-time category	Mean VABS score (SD) - high risk of development impairment	Mean VABS score (SD) - low risk of development impairment	**Mean VABs score (SD) - whole group**	p value	Total
< 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-2 mos.	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
Total					359

*Lead-time to treatment not recorded in 3 cases

ANOVA: F (4, 354) =6.38, Probability > F = 0.0001

Table 2

Results of final multiple linear regression with Vineland Adaptive Behaviour Score as dependant variable

Vineland Adaptive Behaviour Score	Coefficient	95% Confidence Interval	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 aetiology	- 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

[$F(8, 346) = 47.9$, Probability > $F < 0.0001$, $R^2 = 0.53$, n=355]

*Lead-time to treatment not recorded in 3 cases and epilepsy outcome not recorded in 4 cases

Table 3: Epilepsy Outcome (all seizure types) at 18 months*
Multivariable logistic regression

Epilepsy at 18 months	Number with Epileptic seizures at 18 months	Adjusted Odds Ratio (95% CI)	p value
Treatment modality		1.4 (0.8 to 2.3)	0.23
Combination	54/178		
Hormonal	51/177		
Early Clinical Response		0.2 (0.1 to 0.4)	<0.001
Responder	39/228		
Non-responder	66/127		
Developmental Impairment		1.5 (0.9 to 2.6)	0.12
High Risk	71/193		
Low Risk	34/162		
Hormone Type		0.8 (0.4 to 1.4)	0.37
Prednisolone	80/251		
Tetracosactide	25/104		
Hormone Randomised		1.1 (0.6 to 1.8)	
Yes	37/131		
No	68/224		
Lead-time			
< 7 days	27/103	ref	
8-14 days	17/66	0.9 (0.4 to 1.9)	0.8
15-28 days	18/77	0.8 (0.4 to 1.7)	0.64
29 days-2 months	20/58	1.3 (0.6 to 2.8)	0.52
> 2 months	23/51	1.5 (0.7 to 3.3)	0.3

[Likelihood ratio χ^2 55.62, df(9), $p < 0.0001$]

*Lead-time to treatment not recorded in 3 cases and epilepsy outcome not recorded in 4 cases