Safety and efficacy of hormonal treatment versus hormonal treatment with vigabatrin for infantile spasms (ICISS): a multi-centre, open-label randomised trial

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Abstract

Background:

Infantile spasms are a severe infantile epilepsy syndrome that is difficult to treat and have a high morbidity. Hormonal therapies or vigabatrin are the two treatments most commonly used. We investigated whether combining both treatments would be more effective than hormonal therapy alone.

Methods:

In this international, multi-centre, open-label randomised trial, 102 hospitals (Australia [3], Germany [11], New Zealand [2], Switzerland [3], and UK [83]) enrolled infants who had a clinical diagnosis of infantile spasms, a hypsarrhythmic EEG or similar, and were no more than 7 days from clinical diagnosis. Participants were randomly allocated (1:1) by a secure website to receive hormonal therapy with vigabatrin or hormonal therapy alone. Block randomisation was stratified for hormonal treatment and risk of developmental impairment. Parents and clinicians were not blinded to therapy, but investigators assessing electro-clinical outcome were blind to treatment allocation. Minimum doses were prednisolone 10mg qds or IM tetracosactide depot 0·5mg (40iu) on alternate days with or without vigabatrin 100 mg/kg per day. The primary outcome was no observed spasms between days 14 and 42 inclusive of treatment. Analysis was by intention to treat. The trial is registered with The International Standard Randomised Controlled Trial Number (ISRCTN), 54363174.

Findings:

Between March 7, 2007 and July 2, 2014, 766 infants were screened and of those, 377 were randomised to hormonal therapy with vigabatrin (186) or hormonal therapy alone (191). All 377 infants randomised were assessed for the primary outcome. 133 of 186 (71.5%) on hormonal therapy with vigabatrin compared with 108 of 191 (56.5%) on hormonal therapy alone (difference 15%, 95% CI = 5·1% to 24·9%, p = 0·002) had no witnessed spasms between days 14 and 42 inclusive. Serious adverse reactions occurred in 33 cases (17 on hormonal therapy with vigabatrin); there were no deaths attributable to treatment.

Interpretation:

Hormonal therapy with vigabatrin is significantly more effective at stopping spasms than hormonal therapy alone. The definition of response to treatment (absence of spasms from day 14 to 42 inclusive) suggests that the effect seen may be sustained, and this will be investigated at the 18 month follow-up.

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Introduction

Infantile spasms (IS), also known as West syndrome, are a devastating form of infantile epilepsy that is difficult to treat and associated with a poor outcome.[1] It was the first described epileptic encephalopathy – a condition in which the epileptic activity itself contributes to cognitive and neurological decline.[2] Infantile spasms have an estimated incidence of approximately 0·43 per 1000 live births and occur commonly between 3 and 12 months of age with a peak incidence around 6-7 months.[3] There is a characteristic chaotic and high voltage inter-ictal EEG pattern in IS called "hypsarrhythmia" but atypical patterns occur and assessment of the EEG pattern has poor inter-rater reliability.[5,6]

An underlying aetiology, which may be structural (e.g. neuronal migration disorders), genetic (e.g. Down's syndrome), metabolic (e.g. molybdenum co-factor deficiency) or acquired (e.g. hypoxic ischaemic encephalopathy), is identified in 60-70% of cases .[7] This percentage will increase with the advent of newer genetic investigative techniques. Tuberous sclerosis complex is the single most common underlying cause of IS occurring in 7%.

Neuro-development regresses with the onset of this devastating disorder and delayed treatment may lead to worse outcomes.[8-10] Identification of effective, swiftly acting treatments is therefore important. Two treatment modalities have been most investigated: hormonal therapies and vigabatrin. Since 1958, hormonal treatments have been used, initially with intramuscular adrenocorticotropic hormone (ACTH) but more recently with a synthetic

alternative, tetracosactide depot or with oral corticosteroids.[11,12] In the 1990s, vigabatrin, an inhibitor of gamma-aminobutyric acid transaminase, was introduced in Europe as an effective treatment for IS,[13] however, vigabatrin is known to be toxic to the retina and can cause visual field defects. This toxicity in children is estimated to occur in approximately one fifth of those treated and appears to be associated with prolonged treatment of more than 6 months.[14, 15]

We have previously shown that, when compared to vigabatrin, hormonal treatments (prednisolone or tetracosactide depot) are associated with cessation of spasms in a higher proportion of infants, and with superior developmental scores in those infants who have no identified aetiology for their spasms.[12,16,17] We noticed in that trial that there were some children who, having not responded to one treatment, subsequently rapidly responded to the alternate treatment. In the International Collaborative Infantile Spasm Study (ICISS), we aimed to test our hypothesis that combining hormonal and vigabatrin therapy would achieve spasm cessation for 4 weeks between day 14 and 42 of treatment in a greater proportion of infants than with hormonal therapy alone.

Methods

Study design and participants

ICISS was a multicentre, open-label randomised trial with some blind outcome measures, done in 102 hospitals in five countries (Australia [3]: XX; Germany [11]: XX; New Zealand [2]: XX; Switzerland [3]: XX; United Kingdom [83]: XX). Local investigators enrolled and managed patient assessment and care, including determining cessation of spasms.

Participants were included if they were aged 2–14 months at study enrolment; had a clinical diagnosis of infantile spasms as assessed by the local investigator; and had an EEG that was judged by local neurophysiologists to be hypsarrhythmic or similar, compatible with the diagnosis of infantile spasms. Participants were excluded if they were aged less than 2 months or more than 14 months; had a delay of more than 7 days since the diagnosis; had a diagnosis of tuberous sclerosis, previous treatment for infantile spasms or previous use of hormonal treatments or vigabatrin; the coincidence of another condition was likely to be lethal before outcome assessment; there was predictable lack of availability for follow up for 18 months; the parents or guardians had difficulty with language used for assessment; or they were participating in a concurrent trial. Written informed consent was obtained from the parents or guardian.

The study protocol was approved by the UK South West Multicentre Research Ethics Committee (06/MRE06/21) and all relevant local research ethics committees.

Randomisation and masking

Patients were randomized (1:1) to receive hormonal therapy with vigabatrin or hormonal therapy alone. Randomisation was done using an interactive computer system accessed independently by recruiting clinicians via the trial website. Where parents consented, there was an additional randomization of type of hormonal therapy used, (1:1, prednisolone or tetracosactide depot). Block

randomisation (random block size of less than 10) was used and 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 (GT) generated the allocation sequences.

The pre-treatment and post-treatment (obtained between days 14-21 inclusive after initiation of treatment) EEGs were assessed blind to treatment and to clinical outcome: a majority view of three clinicians (JPO, AL, RN, RP) was accepted for determination of the resolution of EEG features supporting the diagnosis. Aetiology was determined blind to treatment (FJKO'C and JPO) through history, examination and investigation and classified as proven (subdivided into prenatal, perinatal, postnatal and other), no aetiology identified, or not known if a major piece of information was missing. A study radiologist (ML) reviewed MRI scans.

Procedures

The study treatments were prednisolone (soluble tablets), tetracosactidedepot , and vigabatrin. Pyridoxine could only be given to exclude pyridoxine dependent seizures. The same products were used in all participating hospitals, 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 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 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 minimum follow up with treating clinicians on days 15 and 43.

Outcomes

The primary outcome was cessation of spasms, which was defined as no witnessed spasms on and between Day 14 and Day 42 inclusive from trial entry.

Secondary outcomes were time to response (defined as the first day after initiation of trial treatment on which spasms were not seen and after which response was maintained until Day 42 of treatment); electro-clinical response (defined as cessation of spasms and resolution of the EEG features supporting the diagnosis i.e. hypsarrhythmia or similar, compatible with the diagnosis of infantile spasms); absence of spasms on days 13 and 14; and number of responders if single spasms are allowed in responders from Day 14 to 42 inclusive.

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 2).

Adverse events were assessed by the local investigator and of these, only adverse reactions were reported to the trial centre. A Data Monitoring and Ethics Committee reviewed recruitment and serious adverse reactions. 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 study investigators (JPO, FOC, SE) who reviewed the case report forms as they were returned to the trial centre (Bath, United Kingdom).

Statistical analysis

Using the data from our previous clinical trial (UKISS)[12,16,17] and using the definition of cessation of spasms described above, we estimated that 60% of infants would achieve a primary clinical response on hormonal therapies. We judged that an improvement in response of 15% (i.e. from 60% to 75%) would be considered clinically meaningful. Consequently the number of participants required to see an improvement from 60% to 75%, using a two-tailed alpha level of 0.05, and 90% power would be 205 in each group, or 150 in each group at 80% power (see ICISS protocol, section 11.2.1). Recruitment commenced on March 7, 2007 and by May 22, 2014, 377 infants had been recruited giving well in excess of 80% power. 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 small number of patients needed to reach 90% power.

All analyses were by intention to treat. The percentages responding to each treatment modality and the difference in percentages with 95% confidence intervals are reported. Differences between the hormonal treatment group and the hormonal treatment with vigabatrin group for the primary outcome were

assessed using logistic regression. Sensitivity analyses controlling for age at randomization, sex, and lead-time to treatment were performed.

This study incorporated a patient preference design whereby prednisolone or tetracosactide depot were allocated either by randomization or patient preference. A further sensitivity analysis was therefore performed to establish whether any main treatment effect was consistent however hormonal treatment was allocated. A final multivariate model was constructed incorporating the main treatment effect, the variables used for stratification in randomisation, and whether hormonal treatment was randomized or not. Logistic regression models were not over-fitted.[18] Statistical analyses were performed using Stata IC 11·2 (Statacorp, College Station, Texas, USA).

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. The full protocol is available at www.iciss.org.uk.

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 ALJ) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The trial ran from March 7, 2007 (date of first recruit) until July 2, 2014 (date of last primary outcome assessment). 766 infants were assessed for eligibility, of whom 377 met the inclusion criteria and were randomised (figure 1). Of these, 186 were allocated to hormonal therapy with vigabatrin (combination therapy) and 191 were allocated to hormonal therapy alone. One infant allocated prednisolone with vigabatrin did not receive vigabatrin and one allocated tetracosactide depot (with vigabatrin) received prednisolone (with vigabatrin). Eight allocated to tetracosactide depot received tetracosactide non- depot (2 with vigabatrin). One case allocated to tetracosactide depot with vigabatrin withdrew and they were categorized as a non-responder for the purposes of this analysis; therefore results from all 377 infants were analysed for the primary outcome.

Of the total 377 infants randomised, the treatment was given according to protocol in 319 (149 on vigabatrin) infants over the first 14 days and in 349 (171 on vigabatrin) infants between days 15 and 42 inclusive. There was reason to suspect non-adherence to treatment in 19 (10 on vigabatrin). Three patients allocated hormonal treatment alone received vigabatrin when tuberous sclerosis was diagnosed in two and at parents request in one. Thirty-two received pyridoxine to exclude pyridoxine dependent seizures (20 on vigabatrin) and seven (four with vigabatrin) received non-trial treatments for their spasms in the first 14 days (all received a benzodiazepine).

The age range at randomization was 73 to 420 days (median 206 days). There were no clinically important imbalances between treatment groups with regard to baseline characteristics (Table 1). At trial entry, 55(30 on vigabatrin) were receiving a concurrent anti-epileptic for other seizure types.

The primary outcome was assessed in 377 infants. Cessation of spasms occurred in 133 of 186 (71·5%) on hormonal treatment with vigabatrin and in 108 of 191 (56·5 %) on hormonal treatment alone (difference 15%, 95%CI 5·1% to 24·9%; chi-squared = 9·15 (1 df), p=0·002).

The treatment effect favouring combination therapy remained significant in a logistic regression analysis that controlled for risk of developmental impairment, type of hormone treatment, and whether or not hormonal treatment was randomized (Odds ratio 2·1 (95% CI 1·3 to 3·2) p = 0·001, Table 2). High risk of developmental impairment was the other variable in the multivariable model that was significantly associated with the primary outcome (Odds ratio 0.4 (95% CI 0·3 to 0·6) p < 0·001, Table 2).

In univariate analyses, the only other variable with a significant relationship with the primary outcome—apart from modality of treatment and risk of developmental impairment—was lead-time to treatment. There was a clear drop in response rate in those infants who had a lead-time to treatment greater than two months (Table 3).

After stratifying the data by risk of developmental impairment, the effects of combination therapy are more clearly seen in those children who were thought at the time of randomization to be at low risk for developmental impairment (n=170). In this group, cessation of spasms occurred in 54 of 87 (62·1%) on hormonal treatment alone and 73 of 83 (88·0%) on combination therapy (difference 25.9%, 95%CI 12.6% to 39.2%, chi squared = 15.1 (1 df), p<0.001). In the group thought to be at high risk of developmental impairment at randomization (n=207), cessation of spasms occurred in 54 of 104 (51·9%) on hormonal treatment alone and in 60 of 103 (58·3%) on hormonal treatment with vigabatrin (difference 6·4%, 95%CI – 7·4% to + 20·2%, chi squared = 0.84 (1 df) p=0·36).

Secondary outcomes were assessed in 377 infants. Treatment response was faster on combination therapy (median response time = 2 days, IQR 2-4 days) than hormonal therapy alone (median response time = 4 days, IQR 3-6 days, z = 6·04, p < 0·001, Wilcoxon rank sum test).

Electro-clinical response was achieved in 227 of the 374 infants in whom both clinical and electrical outcomes were available (three missing values). 123 of 185 (66·5%) allocated to combination therapy compared with 104 of 189 (55·0%) allocated to hormonal therapy alone achieved an electro-clinical response (difference 11·5%, 95% CI 1·4% to 21·6%, chi squared = 5.2 (1 df) p = 0·023). The treatment effect favouring combination therapy with respect to electro-clinical outcome remained in the multivariate logistic regression (Odds ratio 1·7 (95% CI 1·1 to 2·8) p = 0·015, Table 4). Risk of developmental impairment was

also significantly associated with electro-clinical outcome; those thought to be at high risk of developmental delay at randomization had significantly reduced odds of achieving an electro-clinical response compared to the low risk of developmental delay group (Odds ratio 0.5 (95% CI 0.3 to 0.8) p = 0.003).

Cessation of spasms at Days 13 and 14 was achieved in 166 out 186 (89.3%) infants treated with combination therapy compared with 132 out of 191 (69.1%) in those treated with hormonal therapy alone (difference 20.2%, 95%CI 11.8% to 28.6%; chi-squared = 23.2 (1 df), p < 0·001). 57 out of the 298 (19.1%) day 13 and14 responders had relapsed by Day 42 (33 who had been on combination therapy, and 24 who had been on hormonal therapy alone).

The number of responders if single spasms are allowed in responders from Day 14 to 42 inclusive were 141 out of 186 (75.8%) on combination therapy compared with 121 out of 191 (63.4%) on hormonal therapy alone (difference 12.4%, 95%CI 2.9% to 21.9%; chi-squared = 6.9 (1 df), p=0·009).

Adverse reactions (table 5) were reported in 228 infants (117 on vigabatrin). Serious adverse reactions occurred in 33 infants (17 on vigabatrin). There were no deaths attributable to trial treatment. Treatment dose was less than expected due to an adverse reaction in 17 infants (14 on vigabatrin). Movement disorders were reported in 16 infants (14 on vigabatrin).

Discussion

As had been hypothesized, hormonal therapy with vigabatrin (combination therapy) compared to hormonal therapy alone was associated with more infants achieving the primary outcome of spasm cessation between days 14 and 42 of treatment. It also resulted in a shorter time to cessation of spasms and more infants achieving electro-clinical response. While the Cochrane review[19] of infantile spasms had determined that hormonal treatment was the best single treatment for the cessation of spasms, this trial has shown that combination therapy is superior to hormonal therapy alone.

The aim in treating children with epilepsies is often to avoid using multiple agents to minimize side effects. This trial is unusual in using combination therapy and showing it to be superior to monotherapy. However, other investigators have also found that combinations of therapy may be the most effective way of treating severe epilepsy syndromes in childhood.[20] Combining hormonal therapy with vigabatrin may have a synergistic effect or it may effectively treat two different populations of infants: those that will preferentially respond to manipulation of GABA levels and those that respond to the mechanisms through which hormonal therapies exert their effect perhaps by

reducing levels of the pro-epileptogenic neuropeptide, corticoptrophin releasing hormone.[21]

The proportion showing a primary clinical response to combination therapy in ICISS (72%) is similar to the proportion showing a primary clinical response to hormonal therapy alone in our previous study, UKISS (73%).[12] However, the definition of cessation of spasms in ICISS is far more stringent than that used in UKISS (absence of spasms for a 48-hour period on Days 13 and 14 after starting treatment in UKISS vs absence of spasms for a four-week period from Day 14 to Day 42 after starting treatment in ICISS). The definition of cessation of spasms used in this trial was arrived at following a Delphi consensus exercise amongst experts prior to writing the trial protocol.[22] If the UKISS definition of clinical response is applied to the data from this trial, then the response rates on both treatment arms is much higher (89.3% versus 69.1%) and the treatment difference (20.2%) between the two arms is even wider. The number of Day 13 and 14 responders who had relapsed by Day 42 (57 out of 298 i.e 19.1%) underlines the validity of using a longer period of time to determine clinical response. The use of such a stringent definition increases confidence that the primary clinical response seen in this trial is both statistically significant and clinically meaningful.

One of the factors used in pre-randomisation stratification was whether there was a perceived risk of developmental impairment. The trial protocol defined this risk as any patient who had a proven chromosomal abnormality, a proven dysmorphic syndrome diagnosis, a proven diagnosis of cerebral palsy, a previous

diagnosis of neonatal encephalopathy with seizures, or a diagnosis of developmental impairment already made before the onset of spasms. The 88% response rate to combination therapy in those children not defined as being at risk of developmental impairment is remarkable given the perceived difficulty in treating this disorder and emphasizes the need to consider combination therapy, especially in those children in this group who can easily be identified as low-risk at the time of diagnosis.

The level of risk of developmental impairment was effectively a proxy for aetiology identified/not identified that could only be defined post-hoc as it depended upon certain investigations which could only be performed after treatment had already been initiated. After analysis of the trial clinical report forms and neuroimaging, the underlying aetiology was proven in 219 cases (58·1%), and no aetiology was identified in 158 cases (41.9%). As expected, there was a strong association between the variables "risk of developmental impairment" and "aetiology identified" (Chi squared = 113.3 (1 df), $p < 0.001$) . We used risk of developmental impairment in our analysis as that had been one of our stratification criteria but the results are very similar if aetiology identified / not identified is used. In the aetiology not identified group, the early clinical response rate to combination therapy was 85·1% and the response rate to hormonal therapy alone was 60·2% (difference 24·9%, (95% CI 10·1% to 39·38%) $p < 0·001$). This result contrasts with the UKISS data, a smaller study where there was no perceived effect of aetiology on rate of cessation of spasms.[12]

Previously, in UKISS, we have shown that longer lead-times to treatment were associated with lower developmental quotients but not with lower rates of spasm cessation.[10,12] The present study, however, suggests that a lead-time of greater than 2 months from spasm onset to treatment is associated with a lower rate of spasm cessation (Table 3). This result emphasizes the need for clinicians to identify and treat infantile spasms as soon as possible.

In this trial, analysis was by intention to treat, and infants were enrolled if their treating physicians believed that the child had infantile spasms based upon clinical observation and having an EEG compatible with the diagnosis. As such, the trial mirrored as closely as possible what would happen in clinical practice and the results of the trial are therefore likely to be relevant to clinicians. Reporting absence of spasms relied upon parental observation, as recorded in a seizure diary, and interpretation of that history by the local clinician. The UKISS trial had been criticized, particularly in North America, because it reported limited electro-clinical outcome information i.e. the cessation of spasms plus the resolution of the hypsarrhythmic EEG or similar.[24] In ICISS, we have reported the electro-clinical outcome and the superiority of combination therapy remains.

There is no definitive evidence that one form of hormonal treatment is better than the other, and in UKISS we found no difference. However, we incorporated both treatments into the trial because we are aware that some clinicians have a preference for one (particularly ACTH) and we felt we would not have had widespread acceptance of the trial if we had excluded tetracosactide. Conversely we were aware that many parents dislike the idea of giving

intramuscular injections and therefore we felt it necessary to include oral prednisolone as a hormonal therapy option. We allowed parents, but not clinicians, to choose their hormonal treatment. This was done to protect recruitment into the trial for our main comparison (hormonal treatment with or without vigabatrin). Therefore it is not possible for us to say, without risk of bias, which hormonal treatment was superior either when used as monotherapy or in combination with vigabatrin. In Table 4 there is a result that suggests prednisolone is associated with significantly less chance of achieving an electro-clinical response than tetracosactide (Odds ratio 0.6 (95% CI 0.4 to 1.0) p = 0.04) ,but because of the lack of randomization of hormonal therapy, we feel this result should be interpreted with caution.

Adverse reactions are a clinically significant problem with both treatments, but no significant differences exist between the groups. There were no deaths attributable to treatment in this trial. Previously there has been concern that high dose hormonal therapy will impair infants' ability to fight infection and predisposes them to overwhelming sepsis.[25] The lack of any such events in this trial may reflect a better standard of care for patients involved in a clinical trial. As recommended in the trial protocol, we would strongly advise antibiotic treatment, including anti-staphylococcal agents, for any child on hormonal treatment who becomes febrile.

Retinal toxicity from vigabatrin therapy and consequent visual field defects (VFDs) are a legitimate concern. It is impossible to tell whether vigabatrin therapy in this trial will have led to any defects, but as VFDs appear to be

associated with prolonged therapy, the risk of VFDs in this trial where treatment with vigabatrin ceased after 4 months is likely to have been low[14,15]. Jammoul et al. first suggested that vigabatrin mediated retinal toxicity was caused by taurine deficiency and suggested taurine supplementation in infants receiving vigabatrin[26]. This recommendation was made two years after the trial started and we did not therefore mandate taurine supplementation for those receiving vigabtrin. It is possible that some infants will have received taurine but we did not record this in the trial.

Movement disorders were reported to us during the trial and were an unexpected adverse event. We have already reported on the first ten infants notified to us since this was felt to be an important issue.[27] We concluded that it was not possible to attribute movement disorders to vigabatrin and that they were likely related to underlying neurological disease. We did not find that movement disorder was related to the MRI changes associated with vigabatrin therapy.

ICISS represents the largest study or clinical trial of infantile spasms undertaken to date. The obvious strengths of the trial are that it was adequately powered and that treatments were randomized. Other strengths were the complete follow-up of all 377 infants for the primary outcome, its inclusion criteria that closely mimic clinical practice, its stringent definition of the primary clinical outcome, and its blind assessment of EEG outcomes. There are, however, some unavoidable limitations. Neither patients nor clinicians were blind to treatment allocation. In infants it would not be possible to blind allocation to tetracosactide

depot, which is given by intramuscular injection. Conceivably, hormonal therapy with vigabatrin could have been compared to hormonal therapy with placebo but the costs of furnishing trial supplies to all sites for the duration of the trial were prohibitive for a non-commercial trial. Clinicians assessing the primary clinical outcome were not blinded to treatment allocation, but this would never have been possible given that treatment outcome was assessed over a four week period by patient diary. Assessors of the electro-clinical outcome were, however, blind to treatment allocation and the association between combination therapy and improved outcome remained.

A further potential weakness in the study is that investigators, despite the directions of the protocol, did not universally record reasons for exclusion amongst children who were screened for the study. This could theoretically have introduced a selection bias if individual clinicians were systematically biased with respect to enrolling some children and not others into the trial. However, we think such a bias is unlikely. Firstly, the profile of the trial participants in terms of sex, age, proportion with developmental delay at onset, and aetiologies was similar to the UKISS trial and to previous epidemiological (population based) cohorts of infantile spasm patients.[3] Secondly, a total of 151 clinicians from 102 sites were responsible for enrolling the 377 patients in the trial across five countries with the median number of recruits per centre being two and therefore it is difficult to see how any one clinician's bias with respect to recruitment in the trial would be likely to have a significant impact on the overall trial. Thirdly, the recruitment rate of approximately 50% of all patents screened

compares favourably with previous trials in this area and with other trials in similar rare diseases.

Although all 377 infants were followed up for the primary clinical outcome, three children did not have EEG data for an electro-clinical outcome. It is unlikely that such a small number of missing data will have altered the result seen. Even if all three children are classified as non-responders for the electro-clinical outcome then the significant result favouring combination therapy remains.

The most obvious question to be resolved by future research is whether combination therapy is associated not only with improved rates of spasms cessation but also improved development. The rationale for wanting to treat IS as rapidly and effectively as possible is because the spasms are distressing and also because by doing so we may improve developmental outcome by shortening the exposure to the epileptic encephalopathy. We will attempt to answer this question when we are able to report on the developmental outcome in this cohort at 18 months of age. Beyond the ICISS trial, it will be important to determine whether prednisolone or tetracosactide depot is more effective when combined with vigabatrin. The fact that hormonal therapies were predominantly not randomized in this trial precludes a reliable answer to that question from this data set but it remains an important question to resolve. In North America there still remains a belief, albeit on imperfect evidence, that use of ACTH is preferable to oral corticosteroids.[28,29] Although the majority of infants in this study obtained a clinical response, there is still a significant minority who did not respond to combination therapy and the question of what is the next line of

therapy for non-responders is unclear. Finally, there has recently been a number of genes associated with the development of IS and increasing knowledge of the mode of action of their gene products.[30-32] Specific therapies targeted to specific genetic defects may be a promising avenue for research but the results may not be relevant for the majority of IS cases for whom combination therapy is likely to be the best initial option for treatment.

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 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 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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Research in context:

Evidence before this study:

We have conducted a Cochrane systematic review into the treatment of infantile spasms[17] that we have continued to update to 31 December 2015. In identifying research in the area we search the Cochrane Epilepsy Group Specialised Register (31 December 2015), CENTRAL, MEDLINE (up to 31 December 2015), and the reference lists of all retrieved articles. We used the search terms "infantile spasms" "West syndrome" "West's syndrome", "salaam spasm", "hypsarrhythmia", "randomized controlled trial", "controlled clinical trial", and "clinical trial". There were no language restrictions to the search. We have found 19 small RCTs (fewer than 100 patients enrolled) and 2 larger RCTs (more than 100 patients enrolled) that have looked at a total of 12 different pharmaceutical agents. Overall there are problems with the methodological quality of the studies: only two studies had > 100 participants and only one of the studies was adequately powered. Only 7 stated their method of randomization and only 4 reported concealment of allocation. The most popular and commonly used treatment modalities are either hormonal treatments (prednisolone, natural or synthetic ACTH) or vigabatrin. The strongest evidence suggests that hormonal treatment (prednisolone or tetracosactide depot) leads to resolution of spasms faster and in more infants than does vigabatrin, although responses without subsequent relapse may be no different.[11] The same study suggests that hormonal treatments might improve the long-term developmental outcome compared with vigabatrin in infants not found to have an underlying cause for their spasms.[15,16] There is no conclusive evidence of superiority for any particular type of hormonal therapy (i.e. ACTH versus oral prednisolone), although a recent RCT comparing oral prednisolone versus IM ACTH suggested prednisolone was more effective at achieving electro-clinical remission.[33]

Added value of this study:

This study, with 377 randomised paticipants, is the largest treatment trial of infantile spasms to date. It is the first study to trial a combination of therapies (hormonal therapies plus vigabatrin) versus the current therapeutic modality with the best evidence for effectiveness. It also uses a stringent criteria for clinical and electroclinical outcome that is relevant to clinical practice. It has found that combination therapy is more effective and faster at achieving both clinical and electro-clinical responses in children with infantile spasms.

Implications of all the available evidence:

This study has implications for clinicians treating children with infantile spasms. It suggests a modality of treatment that will stop spasms faster and in more children than has previously been achieved with existing treatment strategies and therefore will potentially lessen the long-term detrimental impact of this devastating epileptic encephalopathy on both development and future epilepsy control.

Table 1. Baseline demographic and clinical characteristics

	Prednisolone (131)	Tetracosactide Depot (60)	**Total Hormonal Alone (191)**	Prednisolone with vigabatrin (135)	Tetracosactide Depot with Vigabatrin (51)	**Total Hormonal with vigabatrin (186)**
Sex						
Female	53 (40%)	27 (45%)	**80 (42%)**	59 (44%)	28 (55%)	**87 (47%)**
Male	78 (60%)	33 (55%)	**111 (58%)**	76 (56%)	23 (45%)	**99 (53%)**
Age at randomisation In days						
60-119	6 (5%)	2 (3%)	**8 (4%)**	9 (7%)	8 (16%)	**17 (9%)**
120-179	40 (31%)	17 (28%)	**57 (30%)**	31 (23%)	11 (22%)	**42 (23%)**
180-239	38 (29%)	25 (42%)	**63 (33%)**	51 (38%)	19 (37%)	**70 (38%)**
>=240	47 (36%)	16 (27%)	**63 (33%)**	44 (33%)	13 (25%)	**57 (31%)**
Lead time to Treatment						
Up to 7 days	42 (32%)	14 (23%)	**56 (29%)**	40 (30%)	14 (27%)	**54 (29%)**
8-14 days	21 (16%)	15 (25%)	**36 (19%)**	23 (17%)	13 (25%)	**36 (19%)**
15-28 days	30 (23%)	12 (20%)	**42 (22%)**	27 (20%)	10 (20%)	**37 (20%)**
29 days to 2 months	13 (10%)	14 (23%)	**27 (14%)**	25 (19%)	8 (16%)	**33 (18%)**
More than 2 months	24 (18%)	5 (8%)	**29 (15%)**	18 (13%)	6 (12%)	**24 (13%)**
Not known	1 (1%)	0	**1 (1%)**	2 (1%)	0	**2 (1%)**
Risk of developmental impairment						
Yes	72 (55%)	32 (53%)	**104 (54%)**	72 (53%)	31 (61%)	**103 (55%)**
No	59 (45%)	28 (47%)	**87 (46%)**	63 (47%)	20 (39%)	**83 (45%)**
Anti epileptic drugs for other seizure types						
None	113 (86%)	53 (88%)	**166 (87%)**	113 (84%)	43 (84%)	**156 (84%)**
One	15 (11%)	5 (8%)	**20 (10%)**	13 (10%)	6 (12%)	**19 (10%)**
2 or more	3 (2%)	2 (3%)	**5 (3%)**	9 (7%)	2 (4%)	**11 (6%)**
Pyridoxine given to exclude dependent seizures	9 (7%)	3 (5%)	**12 (6%)**	13 (10%)	7 (14%)	**20 (11%)**

Table 2: Logistic regression model for primary clinical outcome

Clinical Response	Number of clinical responders	Adjusted Odds Ratio (95% CI)	p value
Treatment modality		2.1 (1.3 to 3.2)	0.001
Combination	133/186		
Hormonal	108/191		
Developmental Impairment		0.4 (0.3 to 0.6)	< 0.001
High Risk	114/207		
Low Risk	127/170		
Hormone Type		0.7 (0.4 to 1.1)	0.107
Prednisolone	162/265		
Tetracosactide	79/112		
Hormone Randomised		1.2 (0.8 to 2.0)	0.425
Yes	92/136		
No	149/241		

Parameters:

Clinical response (1=response, 0=no response)
Treatment modality (1=combination therapy, 0=Hormonal therapy)
Developmental impairment (1=high risk, 0=lower risk)
Hormone type (1 = prednisolone, 0 = tetracosactide depot)
Hormone randomized (1 = randomly allocated, 0 = hormone chosen)

Number of observations in model: 377
Likelihood ratio Chi^2 (4 degrees of freedom): 30.34, $p < 0.0001$

Table 3

Lead-time to treatment and response rate*

Lead-time category	Non-responder	Responder	**Total**
< 7 days	33 (30%)	77 (70%)	**110**
8-14 days	25 (35%)	47 (65%)	**72**
15-28 days	24 (30%)	55 (70%)	**79**
29 days-2 mos.	22 (37%)	38 (63%)	**60**
> 2 months	30 (57%)	23 (43%)	**53**
Total	**134**	**240**	**374**

Chi^2 for trend = 6.06, df = 1, p = 0.0138

*Lead-time to treatment not recorded in 3 cases (2 non-responders, 1 responder)

Table 4: Logistic regression model for electro-clinical secondary outcome

Electro-clinical Response	Number of electro-clinical responders	Adjusted Odds Ratio (95% CI)	p value
Treatment modality		1.7 (1.1 to 2.8)	0.015
Combination	123/185		
Hormonal	104/189		
Developmental Impairment		0.5 (0.3 to 0.8)	0.003
High Risk	110/204		
Low Risk	117/170		
Hormone Type		0.6 (0.4 to 1.0)	0.04
Prednisolone	151/263		
Tetracosactide	76/111		
Hormone Randomised		1.0 (0.6 to 1.6)	0.981
Yes	85/136		
No	142/238		

Parameters:
Electro-clinical response (1=response, 0=no response)
Treatment modality (1=combination therapy, 0=Hormonal therapy)
Developmental impairment (1=high risk, 0=lower risk)
Hormone type (1 = prednisolone, 0 = tetracosactide depot)
Hormone randomized (1 = randomly allocated, 0 = hormone chosen)

Number of observations in model: 374 (3 with electro-clinical outcome missing)
Likelihood ratio Chi^2 (4 degrees of freedom): 19.05, p = 0.0008

Table 5 Adverse Reactions

Number of infants and percentages with adverse reactions during Days 0-42 from entry inclusive. The bold asterisked numbers in brackets indicate the numbers that were serious adverse reactions. P=prednisolone, T=tetracosactide depot, H=hormonal treatments combined, P&V=prednisolone with Vigabatrin, T&V=tetracosactide depot with Vigabatrin and H&V= hormonal treatments combined also with Vigabatrin. U=an unexpected adverse reaction. # required treatment to prevent infection or was infected

Specific Adverse Reactions	P	T	H	P&V	T&V	H & V
Total study number of infants	**131**	**60**	**191**	**135**	**51**	**186**
Allergic rash or anaphylaxis	0	1 (2%)	1 (1%)	0	0	0
Drowsiness	3 (2%)	0	3 (2%)	33(24%)(*3)	12(24%)(*1)	45(24%)(*4)
Endocrine/Metabolic Disturbance	1 (1%)	1 (2%)	2(1%)	1 (1%)	0	1 (1%)
Fluid/Electrolyte disturbance	13(10%)(*1)	10(17%)(*2)	23(12%)(*3)	7(5%)	5(10%)(*1)	12(6%)(*1)
Gastro-intestinal upset	20(15%)(*1)	6(10%)(*1)	26(14%)(*2)	17(13%)(*1)	6(12%)(*1)	23(12%)(*2)
Hypertonia	3 (2%)(*1)	6 (10%)	9(5%)(*1)	0	3(6%)(*1)	3 (2%)(*1)
Hypotonia	8 (6%)(*1)	0	8(4%)(*1)	4 (3%)	3 (6%)	7 (4%)
Immunosuppression	3 (2%)(*2)	0	3 (2%)(*2)	3(2%)(*2)	0	3 (2%)(*2)
Increased appetite	36 (27%)	15 (25%)	51 (27%)	25 (19%)	10 (20%)	35 (19%)
Infection	11(8%)(*4)	8(13%)(*1)	19(10%)(*5)	10(7%)(*4)	4(8%)	14(8%)(*4)
Irritability	54(41%)(*2)	21(35%)(*1)	75(39%)(*3)	45(33%)(*1)	16(31%)(*1)	61(33%)(*2)
Neuropsychiatric (disturbed sleep)	27(21%)(*1)	8(13%)	35(18%)(*1)	22(16%)	7(14%)	29(16%)
Varicella zoster (chicken pox)#	4(3%)(*1)	0	4(2%)(*1)	2(1%)(*1)	0	2(1%)(*1)
Weight gain	23(18%)	11(18%)	34(18%)	16(12%)	8(16%)	24(13%)
(U) Abnormal eye movements	0	0	0	1(1%)	0	1(1%)
(U) Blood disorder - high platelet count	0	0	0	0	1(2%)	1(1%)
(U) Bradycardia	0	0	0	0	1(2%)	1(1%)
(U) Abnormal breathing pattern	1(1%)	0	1(1%)	0	0	0
(U) High signal in basal ganglia	1(1%)	0	1(1%)	2(1%)	0	2(1%)
(U) Hypoxic	1(1%)	0	1(1%)	0	0	0
(U) Movement disorder	2(2%)	0	2(1%)	8(6%)	6(12%)(*3)	14(8%)(*3)
(U) Not focusing	0	0	0	1(1%)	0	1(1%)
(U) Obstructive cardiac hypertrophy	1(1%)(*1)	0	1(1%)(*1)	0	0	0
(U) Pallor	1(1%)	0	1(1%)	0	0	0
(U) Squinting	1(1%)	0	1(1%)	0	0	0
(U) Sweating	0	1(2%)	1(1%)	1(1%)	0	1(1%)
(U) Tachypnoea	1(1%)	0	1(1%)	0	0	0

Figure 1. Trial Profile

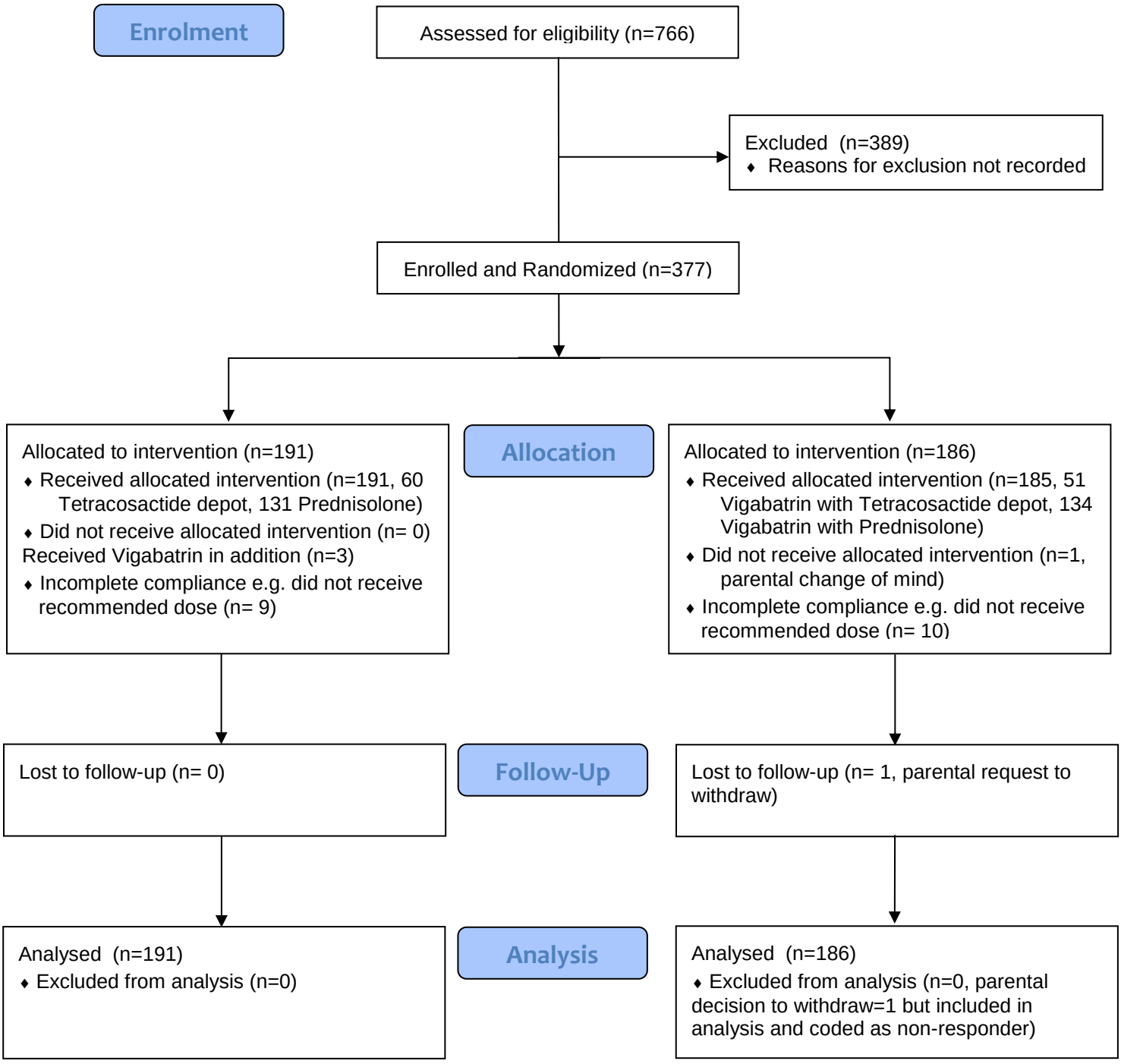
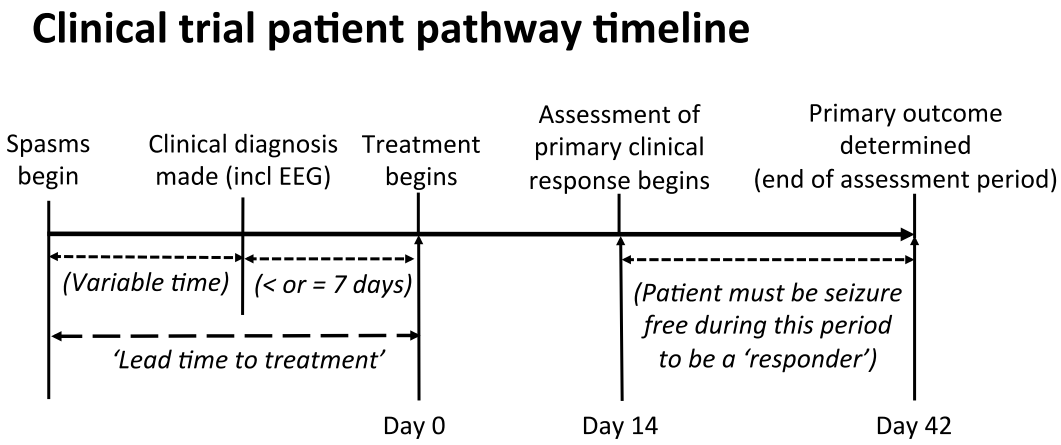


Figure 2


Clinical trial patient pathway timeline
Spasms begin
Clinical diagnosis made (incl EEG)
Treatment begins
Assessment of primary clinical response begins
Primary outcome determined (end of assessment period)
(Variable time)
(< or = 7 days)
'Lead time to treatment'
(Patient must be seizure free during this period to be a 'responder')
Day 0
Day 14
Day 42