The International Collaborative Infantile Spasms Study comparing hormonal treatment (prednisolone or tetracosactide depot) alone to hormonal treatment with vigabatrin: early outcome of a multi-centre randomized controlled trial.

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**Abstract**

Background:

Infantile spasms is a severe epilepsy syndrome of infancy. It is considered difficult to treat and has a high morbidity. We have previously shown that hormonal treatments (either prednisolone or tetracosactide depot) are superior to vigabatrin in eliminating spasms in the short-term and also, in the subgroup of infants with no identified aetiology for their epilepsy, in improving developmental outcome. We aimed to further improve outcome by combining hormonal with Vigabatrin treatment from the outset.

Methods:

We assessed combination therapy in an international multi-centre, randomised, controlled trial. 103 hospitals enrolled (Australia 3, Germany 11, New Zealand 2, Switzerland 3 and UK 84). Infants aged 3 to 13 months diagnosed within the previous week with infantile spasms and an EEG that was hypsarrhythmic or similar were randomly allocated to hormonal treatments or hormonal treatments plus vigabatrin and stratified by which of the two hormonal treatments was given and by whether the risk of developmental impairment was high or low. Minimum doses were oral prednisolone 10mg qds or IM tetracosactide depot 0.5mg (40iu) on alternate days with or without oral Vigabatrin 50 mg bd. The early outcome, cessation of spasms, was defined as no observed spasms between days 14 and 42 inclusive. Treatment was not blinded and analysis was by intention to treat. The ISRCTN was 54363174.

Findings:

377 infants were randomly assigned to hormonal treatment alone (191) or combination therapy (186). There were no deaths and 1 case withdrew and outcomes were assessed in the remaining 376. Of 133 infants allocated to combination therapy, 185 (72%) had cessation of spasms compared to 108 of 191 (57%) allocated to hormonal therapy alone (difference 15.3%, 95% CI 5.4% to 25.2%, chi2 = 9.6, p = 0.002). Serious adverse reactions occurred in 17 (9%) in each group.

Interpretation:

Using a robust definition of response in a large study, cessation of spasms was more likely with combination therapy. Better control of spasms may lead to improved development.

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**Introduction**

Infantile spasms, also known as West syndrome, are a devastating form of infantile epilepsy that is difficult to treat and associated with a poor outcome. It was the first described epileptic encephalopathy – a condition in which the epileptic activity itself contributes to cognitive and neurological decline[[1](#_ENREF_1)]. 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[[2](#_ENREF_2)]. The spasms, which may be flexor, extensor or both, occur in clusters often around the time of waking. Their onset coincides with developmental arrest or regression in many[[3](#_ENREF_3)]. The chaotic and high voltage inter-ictal EEG pattern in IS is often called “hypsarrhythmia” but there is poor inter-rater reliability in recognizing and characterizing the EEG pattern precisely[[4](#_ENREF_4) [5](#_ENREF_5)].

In the majority of cases there is a known underlying aetiology for the IS which may be structural (e.g. neuronal migration disorders), genetic (e.g. Down’s syndrome) metabolic (e.g. non-ketotic hyperglycinaemia) or acquired (e.g. hypoxic ischaemic encephalopathy)[[6](#_ENREF_6)]. Tuberous sclerosis complex is the single most common underlying cause of IS. However, in 30-40% of cases a cause is not found[[6](#_ENREF_6)].

Neuro-development regresses with the onset of this devastating disorder and there is evidence that delaying treatment can lead to worse outcomes. Identification of effective, swiftly acting treatments is therefore an important goal. [[7-9](#_ENREF_7)]. 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[[10](#_ENREF_10) [11](#_ENREF_11)]. In the 1990s, vigabatrin, an inhibitor of gamma-aminobutyric acid transaminase, which is the enzyme responsible for the catabolism of GABA in the brain, was introduced in Europe as an effective treatment for infantile spasms[[12](#_ENREF_12)]. However, in 1997 visual field defects secondary to retinal toxicity were found in 30 % of adults treated with the drug[[13](#_ENREF_13)]. The incidence of vigabatrin associated retinal toxicity in infants treated with the drug for infantile spasms has been estimated at approximately 21% and its occurrence appears to be related to length of treatment (i.e. > 6 months)[[14](#_ENREF_14)].

Our research group has previously shown that hormonal treatments (prednisolone or tetracosactide) when compared to vigabatrin are associated with cessation of spasms in higher proportion of infants and with superior developmental scores in those infants who have no identified aetiology for their spasms[[11](#_ENREF_11) [15](#_ENREF_15) [16](#_ENREF_16)]. The observation, in the course of that trial that there were some children who had not responded to one treatment who frequently and rapidly responded to the alternate treatment when switched over, led us to hypothesise that combining hormonal and vigabatrin therapy would lead to cessation of spasms in a higher proportion of infants than hormonal therapy alone. To investigate the hypothesis we conducted an international multicenter randomized parallel group pragmatic controlled trial: the International Collaborative Infantile Spasm Study (ICISS). In this paper we report on the primary and secondary outcomes at six weeks i.e control of clinical spasms, time to clinical response and electroclinical response (i.e. control of spasms plus resolution of diagnostic EEG).

**Methods:**

Study design:

ICISS was a pragmatic multicentre parallel group open-label trial with some blind outcome measures. Local investigators enrolled and managed patients including determining 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 ISRCTN was 54363174 and the EUDRACT Number was 2006-000788-27. The full protocol is available at [www.iciss.org.uk](http://www.iciss.org.uk).

Participants:

Inclusion criteria were a clinical diagnosis of infantile spasms by the local investigator and an EEG that was hypsarrhythmic or similar, compatible with the diagnosis of infantile spasms. Exclusion criteria were: age under 2 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, and difficulty with language used for assessment or participation in a concurrent trial. Pyridoxine could only be given to exclude pyridoxine dependent seizures. Written consent was obtained from the parents or guardian.

Randomisation and masking:

We allocated treatment by block randomisation (random block size of less than 10) and randomization was stratified on two variables: presence (or not) 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 delay diagnosed before onset of spasms) and hormonal treatment (one of prednisolone or tetracosactide depot) randomly allocated (where parents consented) or chosen by parents. An independent statistician (GT) generated the allocation sequences.

Procedures:

The study treatments were prednisolone (soluble prednisolone tablets, Sovereign Medical, Basildon, in the UK), tetracosactide (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 but the market authorization holder varied. Prednisolone was given orally (10 mg four times a day for 2 weeks, increasing to 20 mg three times a day after 1 week if spasms continued). Tetracosactide depot was given intramuscularly (0·5 mg [40 IU] on alternate days for 2 weeks, and increased to 0·75 mg [60 IU] on alternate days after 1 week if spasms continued). 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, 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. 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, and then every 3 months until a final assessment at 18 months of age.

Pharmacovigilance:

Adverse events were assessed by the local investigator and only adverse reactions were reported to the trial centre. Expected adverse reactions were listed in the protocol. During and immediately after hormonal treatment, the used of antibiotics including an anti-staphylococcal agent was recommended for the treatment of fever. Central monitoring of data was undertaken by (JPO, FJKO’C, SE) who reviewed the case report forms as they were returned to the trial centre in Bath.

Outcomes:

The primary outcome was cessation of spasms defined as no witnessed spasms on Day 14 to Day 42 inclusive. Secondary outcomes included time to response and electroclinical response (cessation of spasms and resolution of the EEG features supporting the diagnosis i.e. hypsarrhythmia or similar, compatible with the diagnosis of infantile spasms). The pre-treatment and post treatment (on and between Days 14-21) EEGs were assessed blind to treatment and to clinical outcome: a majority view of three (AL, RN, JPO, RP) was accepted for determination of the resolution of EEG features supporting the diagnosis. Aetiology was determined by JPO and FJKO’C 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. ML reviewed MRI scans. Lead-time refers to the delay between clinical onset of spams 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.

Statistical Analysis:

With control of spasms as the primary outcome and a difference in effect of 15% or greater (from 60% to 75%) regarded as clinically important, 410 infants were needed to give 90% power and 300 infants to give 80% power at a significance level of 0.05 and two-sided testing.

All analyses, including adverse reactions, were by intention to treat. The percentages responding to each treatment modality, the difference in percentages and 95% confidence intervals are calculated and reported. Logistic regression was used for the primary analysis of hormonal treatment compared to hormonal treatment plus vigabatrin and the effect of this treatment allocation on the early primary clinical outcome. Sensitivity analyses were used to examine possible effects of age at randomization, sex, and lead-time to treatment. Because the choice between prednisolone or tetracosactide was made either by random allocation or by patient preference, a further sensitivity analysis was undertaken to establish whether any main treatment effect was consistent between these two allocation methods. A final multivariate model was constructed incorporating the main treatment effect, the variables used for stratification at randomization, the method of allocation of hormonal treatment, and those variables that on univariate analysis had a strong relationship with outcome. Statistical analyses were performed using Stata IC 11·2 (Statacorp, College Station, Texas, USA).

Recruitment commenced in March 2007 and was again seriously delayed by the bureaucratic hurdles associated with research governance (see discussion). By May 31st, 2014, 377 infants had been recruited giving well in excess of 80% power and the decision was taken to halt recruitment, given the disproportionate costs and renewed applications for funding that would be required to extend the trial to recruit a small number of patients to reach 90% power. A data monitoring and ethics committee reviewed serious adverse events. The ISRCTN was 54363174 and the EUDRACT Number was 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 had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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**Results**

Between March 2007 and May 2014, 733 infants were assessed for eligibility and 377, including 210 male infants, were allocated a randomised treatment at 103 hospitals in five countries (Australia 3, Germany 11, New Zealand 2, Switzerland 3 and UK 84). The trial profile is shown in Figure 1. There were no clinically important imbalances between treatment groups with regard to their baseline characteristics (Table 1). Treatment allocation was to hormonal treatment alone in 191 and to hormonal treatment and Vigabatrin in 186. One case allocated Tetracosactide with Vigabatrin withdrew and they were categorized as a non-responder for the purposes of this analysis and therefore results from all 377 were analysed. One infant allocated Vigabatrin did not receive it and one allocated tetracosactide depot and Vigabatrin received prednisolone and Vigabatrin. Eight, including two that also received Vigabatrin, were allocated tetracosactide depot but received tetracosactide. At trial entry, 54, including 29 allocated to hormonal treatment plus Vigabatrin, were receiving a concurrent anti-epileptic for other seizure types.

The treatment was given according to protocol in 319, including 149 on hormonal treatment with Vigabatrin, over the first 14 days and in 349, including 171 on hormonal treatment with Vigabatrin, between days 15 and 42 inclusive. There was reason to suspect non-adherence to treatment in 19, including 10 on homonal treatment with 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, including 20 on hormonal treatment with Vigabatrin, and seven, four with hormonal treatment with Vigabatrin, received non-trial treatments for their spasms in the first 14 days (all received a benzodiazepine).

Cessation of spasms occurred in 108 of 191 (56·6%) on hormonal treatment alone and in 133 of 185 (71·9%) on hormonal treatment with Vigabatrin (difference 15·3%, 95%CI 5·4% to 25·2%, p=0·002). 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).

The treatment effect favouring combination therapy remained strong in a logistic regression analysis controlling for risk of developmental impairment, type of hormone treatment, lead time to treatment, and whether or not hormonal treatment was randomized (Odds ratio 2·1 (95% CI 1·3 to 3·3) p = 0·001). There was no interaction between method of allocation of hormonal therapy and the main treatment effect. Age at randomization and sex were not included in the model because on univariate analysis they had no relationship with outcome.

On univariate analyses, the only variables with a strong relationship with the outcome, apart from treatment allocation at randomisation, were risk of developmental impairment and lead-time (see methods) to treatment. These relationships remained strong in the multivariate model. There was a clear drop in response rate in those infants who had a lead-time to treatment greater than two months (see Table 2).

Stratifying the data by risk of developmental impairment, the effects of combination therapy are even more clearly seen in those children who were not thought, at the time of randomization, to be at high risk for developmental impairment. In this group cessation of spasms occurred 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%, p<0.001). In the group thought at randomization to be at high risk of developmental impairment, 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%, p=0·36).

After analysis of the trial clinical report forms and neuroimaging (FJKOC, JPO, ML) the underlying aetiology was proven in 219 cases (58.1%) and no aetiology was identified in 158 cases. There was, as expected, a high correlation between risk of developmental delay and aetiology identified. 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 39.4%, p < 0.001).

Electro-clinical response was achieved in 227 of the 374 infants in which both clinical and electrical outcomes were available. Of the responders, 123 of 185 (66.5%) had been allocated combination therapy compared with 104 of 189 (55.0%) allocated to hormonal therapy alone (difference 11·5%, 95% CI 1·4% to 21·6%, p = 0·02). Multivariate logistic regression analysis confirmed this benefit with an odds ratio of 1·7 (95% CI 1·12 to 2·62) p = 0·013 of electro-clinical resolution associated with allocation to combination therapy.

Adverse events (see table 3) were reported in 229 infants (117 on Vigabatrin). Serious adverse reactions occurred in 34 infants (17 on Vigabatrin). There were no deaths. Treatment was lower than expected due to an adverse reaction in 18 (15 on Vigabatrin). Movement disorders were reported in 22 infants, including 14 who were on hormonal therapy with vigabatrin. Of the 22 cases, 16 were reported as adverse reactions.

**Discussion:**

The hypothesis was confirmed that allocation to the combination of hormonal therapy with Vigabatrin was associated with more infants achieving both a clinical and electroclinical response, and more quickly, than was observed after allocation to hormonal therapy alone. Furthermore response to treatment was poorer when started after a longer time interval after the onset of spasms. Whereas the Cochrane review of infantile spasms had determined that hormonal treatment was the best single treatment for the cessation of spasms[[17](#_ENREF_17)], the present study has shown that combination therapy is superior to hormonal therapy alone. These new findings are clinically important.

This trial is unusual in using combination therapy and showing it to be superior to monotherapy since the aim in treating children with epilepsies is often to avoid using multiple agents so as to minimize unwanted effects. However, other investigators have also found that combinations of therapy may be the most effective way of treating severe epilepsy syndromes in childhood[[18](#_ENREF_18)]. 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 (e.g. by reducing levels of the pro-epileptogenic neuropeptide, corticoptrophin releasing hormone)[[19](#_ENREF_19)].

Although 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%)[[11](#_ENREF_11)], the definition of cessation of spasms in ICISS (viz. absence of spasms for a four-week period from Day 14 to Day 42 after the initiation of treatment) is far more stringent than that used in UKISS (absence of spasms for a 48-hour period on Day 13 and 14 after starting treatment). The definition of cessation of spasms used in ICISS was arrived at amongst experts prior to writing the trial protocol by a Delphi consensus method [[20](#_ENREF_20)]. The use of such a stringent definition increases confidence that the primary clinical response seen in this trial is robust.

A high perceived risk of developmental impairment (see methods) was used to stratify participants at randomization. The 88% response rate to combination therapy of those children not meeting the criteria for this risk being perceived to be high is remarkable given the perceived difficulty in treating this disorder and emphasizes the benefit of combination therapy, especially in this subgroup of affected infants. The category high perceived risk of developmental impairment (or not) was a proxy for the category aetiology identified (or not) that could only be defined post-hoc as it depended upon the results of investigations some of which only became available after treatment had already been allocated. We used risk of developmental delay for stratification and this informed our statistical analysis but the results are very similar if the variable, aetiology identified (or not) is used. This effect of aetiology on response to treatment contrasts with the UKISS data, where there was no perceived effect of aetiology on rate of cessation of spasms[[11](#_ENREF_11)].

Previously, in the UKISS data, we have shown that longer lead-times to treatment were associated with lower developmental quotients[[9](#_ENREF_9)] but not with lower rates of cessation of spasms[[11](#_ENREF_11)]. 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 cessation of spasms (Table 2) and if this finding is confirmed at 18-month follow-up, it could be due to prolonged uncontrolled seizure activity prior to diagnosis increasing the likelihood of long-term seizure activity sometimes referred to as kindling [[21](#_ENREF_21)]. This result emphasizes the need for clinicians to identify and treat spasms as early as possible.

Infants were enrolled if their treating physicians believed that the child had infantile spasms on the basis of clinical and EEG features compatible with the diagnosis. The reporting of spasms (or their absence) relied upon parental observation, as recorded in a seizure diary, and interpretation of that history by the local clinician. Many centres in Europe and Australasia will make treatment decisions based upon clinical response without EEG confirmation that hypsarrhythmia has resolved. In ICISS, the electroclinical outcome confirms the superiority of combination therapy also shown clinically, a question that the previous UKISS trial was unable to address[[22](#_ENREF_22)]. In these ways, ICISS was a pragmatic trial which mirrored clinical practice closely and analysis was by intention to treat. The trial and its findings are therefore likely to be generalizable and clinically relevant.

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), as many parents dislike the idea of giving intramuscular injections. 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.

Adverse reactions are a significant problem with both treatments but do not seem to be more of an issue with combination therapy. The death rate, that did not include any deaths attributable to trial treatment, was low for a cohort of children with infantile spasms. Previously there has been concern that high dose hormonal therapy will predispose infants to overwhelming sepsis[[23](#_ENREF_23)]. The lack of any such events in this trial may reflect a better standard of care for patients involved in a clinical trial. We would strongly advise antibiotic treatment, including anti-staphylococcal agents, (see methods) for any child on hormonal treatment who becomes febrile.

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[[24](#_ENREF_24)]. 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.

As an investigator-led non-commercial trial of therapies into an important but relatively rare neurological condtion, ICISS faced significant and unnecessary bureaucratic difficulties and delay. Since IS are often treated in local hospitals and only referred to regional centres for additional investigations or when treatment fails, it was necessary to open large numbers of centres with a low chance of recruiting a case in the time available. Research and development departments in the UK often sought to stop recruitment because of low accrual rates even though the rarity of the condition meant that higher rates of entry to the trial at individual centres were not expected. Recruitment was subject to avoidable because individual centres had to come off-line every time a PI changed due to sickness, retirement or job changes. Individual hospital pharmacies often delayed approvals as they evidently did not understand the concept of pragmatic non-commercial trials. The trial was twice inspected by regulatory authorities, MHRA and Swiss Medic, and, whilst their reports commended the trial, the costs of the inspection to the trial team both in terms of time and money were considerable. Some of these hurdles were unnecessary and are in danger of deterring investigators from embarking on non-commercial trials in the future and that would inevitably be to the detriment of patients.

ICISS represents the largest study or clinical trial of IS ever undertaken. Apart from its size, its obvious strengths are its pragmatic character that closely mimics 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, which is given by intramuscular injection. Conceivably, hormonal therapy plus vigabatrin could have been compared to hormonal therapy plus placebo but the costs of furnishing trial supplies to all international 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.

The rationale for wanting to treat IS as rapidly and effectively as possible is that this may improve developmental outcome by shortening the exposure to the epileptic encephalopathy. We will attempt to provide an insight into the question of whether combination therapy is associated not only with improved rates of spasm cessation but also higher development quotients when we are able to report on developmental outcome in this cohort.

Among question to be addressed by future research there is first the question of which form of hormonal therapy is superior. In North America there still remains a belief that use of ACTH is preferable to oral corticosteroids[[25](#_ENREF_25)] but evidence is lacking and future research should address the question of whether prednisolone or tetracosactide is superior to the other when combined with vigabatrin. The fact that hormonal therapies were predominantly not randomized in this trial precludes a reliable answer to that question from the present data set. Second, there is still a significant minority of infants with IS who do not respond to hormonal treatments alone or with Vigabatrin and the best next line of therapy for non-responders remains unclear. Third, 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[[26-28](#_ENREF_26)]. 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.

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 **Table 1 Baseline characteristics**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Prednisolone** | **Tetracosactide****depot**  | **Hormonal alone** | **Prednisolone****with vigabatrin** | **Tetracosactide****with vigabatrin** | **Hormonal****with vigabatrin** |
| **N (%)** | 131 (100) | 60 (100) | **191 (100)** | 134 (100) | 52 (100) | **186 (100)** |
|  |  |  |  |  |  |  |
| **Female** | 53 | 27 | **80 (42)** | 59 | 28 | **87 (47)** |
| **Developmental** **impairment risk** |  |  |  |  |  |  |
| **Yes** | 72 | 32 | **104 (54)** | 72 | 31 | **103 (55)** |
| **No** | 59 | 28 | **87** | 62 | 21 | **83** |
| **Age at randomisation** |  |  |  |  |  |  |
| **60-119 days** | 6 | 2 | **8** | 9 | 8 | **17** |
| **120-179 days** | 40 | 17 | **57** | 31 | 11 | **42** |
| **180-239 days** | 38 | 25 | **63** | 50 | 20 | **70** |
| **≥240 days** | 47 | 16 | **63** | 44 | 13 | **57** |
| **Lead time to Treatment** |  |  |  |  |  |  |
| **≤7 days** | 42 | 14 | **56** | 40 | 14 | **54** |
| **8-14 days** | 21 | 15 | **36** | 23 | 13 | **36** |
| **15-28 days** | 30 | 12 | **42** | 27 | 10 | **37** |
| **29 days to 2 months** | 13 | 14 | **27** | 24 | 9 | **33** |
| **> 2 months** | 24 | 5 | **29** | 18 | 6 | **24** |
| **Not known** | 1 | 0 | **1** | 2 | 0 | **2** |
| **Other anti epileptic drugs**  |  |  |  |  |  |  |
| **None** |  |  |  |  |  |  |
| **One** | 15 | 5 | **20** | 13 | 5 | **18** |
| **2 or more** | 3 | 2 | **5** | 9 | 2 | **11** |
| **Pyridoxine given**  | 10 | 3 | **13** | 14 | 8 | **22** |

**Table 2 Response (cessation of spasms) by lead-time to treatment**

|  |  |  |  |
| --- | --- | --- | --- |
| **Lead-time category** | **Non-responder** | **Responder** | **Total** |
| **n** | **134** | **240** | **374** |
| **< 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** |

Pearson Chi2 = 12.7, p = 0.013

**Table 3 Numbers of infants with adverse reactions in first 42 days**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Specific Adverse Reactions** | **P** | **T** | **H**  | **P&V** | **T&V** | **H & V** |
| **Infants receiving treatment n (%)** | **132 (100)** | **60 (100)** | **191 (100)** | **134 (100)** | **52 (100)** | **186 (100)** |
| Allergic rash or anaphylaxis | 0 | 2 (3%) | 2 (1%) | 0 | 0 | 0 |
| Drowsiness | 3 (2) | 0 | 3 (2%) | 33(25%)(**3**) | 12(23%)(**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(5%)(**1**) | 6(12%)(**1**) | 23(12%)(**1**) |
| 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%) | 0 | 3 (2%) | 3(2%)(**2**) | 0 | 3 (2%)(**2**) |
| Increased appetite | 36 (27%) | 15 (25%) | 51 (27%) | 25 (19%) | 10 (19%) | 35 (19%) |
| Infection | 11(8%)(**4**) | 9(15%)(**2)** | 20(10%)(**6**) | 10(7%)(**4**) | 4(8%) | 14(8%)(**4**) |
| Irritability | 55(42%)(**2**) | 21(35%)(**1**) | 76(40%)(**3**) | 45(34%)(**1**) | 17(33%)(**1**) | 62(33%)(**2**) |
| Neuropsychiatric | 27(20%)(**1**) | 8(13%) | 35(18%)(**1**) | 22(16%) | 7(13%) | 29(16%) |
| Varicella zoster (chicken pox) | 4(3%)(**1**) | 0 | 4(2%)(**1**) | 2(1%)(**1**) | 0 | 2(1%)(**1**) |
| Weight gain | 23(17%) | 11(18%) | 34(18%) | 16(12%) | 8(15%) | 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%) | 1(2%) | 2(1%) | 0 | 0 | 0 |
| None of the above |  |  |  |  |  |  |

The bold numbers in brackets indicate the numbers that were classified as serious adverse reactions. P=prednisolone, T=tetracosactide depot, H=hormonal treatments combined, P&V=prednisolone with Vigabatrin, T&V=tetracosactide depot with Vigabatrin, H&V= hormonal treatments with Vigabatrin. U=an unexpected adverse reaction