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Prednisolone or tetracosactide depot for infantile epileptic spasms syndrome? A prospective analysis of data embedded within two randomised controlled trials

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ABSTRACT

Objective: To report a prospectively planned analysis of two randomised controlled trials with embedded comparisons of prednisolone versus tetracosactide depot for the treatment of infantile epileptic spasms syndrome (IESS).

Methods: Individual patient data from patients randomly allocated to prednisolone or tetracosactide depot were analysed from two trials (UKISS, ICISS). The comparison was embedded within trials in which some patients also received vigabatrin but only patients receiving monotherapy with randomly allocated hormonal treatments are included in this analysis. The main outcome was cessation of spasms (Days 13–14 after randomisation). Lead time to treatment and underlying aetiology were taken into account. Cessation of spasms on Days 14–42 inclusive, electroclinical response (EEG Day 14), plus developmental and epilepsy outcomes (at 14 months in UKISS and 18 months in ICISS) are also reported. Minimum treatment was prednisolone 40 mg per day for two weeks or tetracosactide depot 0·5 mg IM on alternate days for two weeks, all followed by a reducing dose of prednisolone over two weeks.

Results: 126 infants were included in this study. On tetracosactide depot, 47 of 62 (76%) were free of spasms on Days 13–14 compared to 43 of 64 (67%) on prednisolone (difference 9%, 95% CI -7·2% to +25·2%, chi square 1·15, p = 0·28). For Day 14–42 cessation of spasms, on tetracosactide depot, 41 of 61 (67%) were free of spasms compared to 35 of 62 (56%) on prednisolone (difference 11%, 95% CI -6·4% to +28·4%, chi square 1·51, p = 0·22). There was no significant difference in mean VABS score between infants who received prednisolone compared with those who received tetracosactide depot (74·8 (SD 18·3) versus 78·0 (SD 20·2) t = −0·91 p = 0·36). The proportion with ongoing epilepsy at the time of developmental assessment was 20 of 61 (33%) in the

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tetracosactide group compared with 26 out of 63 (41%) in the prednisolone group (difference 8%, 95% CI -9·2% to +25·2%, Chi [2] 0·95, p = 0·33).
Significance: With hormone monotherapy, either prednisolone or tetracosactide depot may be recommended for infantile epileptic spasms syndrome.

1. Introduction

Infantile epileptic spasms syndrome (IESS) is a devastating form of epilepsy associated with a poor outcome both with respect to development and future epilepsy control [1–3]. IESS was the first described developmental epileptic encephalopathy – a condition in which the epileptic activity itself is believed to contribute to cognitive and neurological decline [4]. It is the most common developmental epileptic encephalopathy affecting approximately 1 in 2500 infants [5].

Hormonal treatments, most often prednisolone, adrenocorticotrophic hormone (ACTH) or tetracosactide depot (a synthetic analogue of ACTH), have been used since 1958 but little is known about their relative merits and there are still few data on the best dosage or duration of treatment required to control the spasms [3]. Any underlying neurological aetiology can have a profound and independent effect on development but the lead time to treatment – the time from onset of spasms to start of treatment – also affects developmental outcome [6]. Treatment that effectively stops spasms may also have an effect on developmental outcome but this is less clear [7]. Cessation of spasms may now be best achieved by the use of combined treatment (either hormonal treatment with vigabatrin) [8], but it is still important to know which hormonal treatment, if any, is superior in order to inform use either as monotherapy or when given in combination with vigabatrin.

We have previously undertaken two treatment trials in an attempt to improve the outcome for these infants. The United Kingdom Infantile Spasms Study (UKISS) [9], compared hormonal treatments to vigabatrin. The International Collaborative Infantile Spasms Study (ICISS) [8], compared hormonal treatments with or without vigabatrin. Embedded in these two trials was a second randomisation of hormonal treatments with allocations to either oral prednisolone or intramuscular tetracosactide depot with the prospective intention of combining the results in a separate analysis in due course. We report here the results on spasm cessation as well as developmental and longer-term epilepsy outcomes, comparing prednisolone to tetracosactide depot. These combined results are new.

2. Methods

Randomisation and Masking: The full methods for the studies have been previously published [8,9]. Both UKISS and ICISS were pragmatic multicentre parallel group open-label trials with concealed allocation of treatment and some blind outcome measures. In UKISS (conducted in the UK) and ICISS (conducted in the UK, Australia, Germany, New Zealand and Switzerland) the treatment allocations were concealed but in ICISS the treatment allocation of hormonal treatment (and of vigabatrin) was concealed except that parents who wished to do so were allowed to choose their type of hormonal treatment. This protected recruitment into the main trial comparison of hormonal treatment with or without vigabatrin. Those parents in ICISS whose infants were not allocated vigabatrin and who did not choose their infant's hormonal treatment thus had randomised concealed allocation of their hormonal treatment and only those infants are included in this analysis.

Inclusion and exclusion criteria were similar with the following main exception: in ICISS, use of pyridoxine was specifically excluded except for the identification of pyridoxine dependent seizures. Key features were exclusion in both trials of those infants with tuberous sclerosis or who had previously been treated either for their spasms or with the trial treatments. They were included if aged (inclusive) between 2 and 12 months in UKISS and 2 and 14 months in ICISS.

The study treatments were identical in both studies: prednisolone (soluble prednisolone tablets) and tetracosactide depot (Synacthen Depot). 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. 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.

2.1. Outcomes

The main outcome was cessation of spasms defined as no witnessed spasms on Days 13 and 14 post randomisation. Cessation of spasms on and between Day 14 and Day 42 was also recorded, prospectively in ICISS and retrospectively, from clinical trial records, in UKISS. Electroclinical response was defined as cessation of spasms plus loss of the EEG features supporting the diagnosis of infantile spasms whether hypsarrhythmia or similar (ie: no longer compatible with the diagnosis of infantile spasms): these EEGs were performed between days 14 and 21 in ICISS but between days 12 and 19 in UKISS.

Lead time to treatment was collected prospectively in both UKISS and ICISS but was categorised retrospectively from clinical trial records in UKISS into the five categories used in ICISS. Underlying aetiology was assessed by the local investigator using investigations they considered appropriate, including history (including antenatal, perinatal and postnatal history), examination, fundoscopy, metabolic screen, chromosome analysis and cranial imaging. Infants were classified as having "no identified aetiology" where all appropriate investigations had not revealed an underlying abnormality, and were classified as "aetiology not known" where key information was missing. Developmental assessment was undertaken over the telephone using the Vineland Adaptive Behaviour Scales (VABS) at age 14 months in UKISS (by one assessor, AL) and at age 18 months in ICISS by one of two assessors (AAM for English speaking families and FDA for German speaking families). Epilepsy outcome was undertaken by the local investigator in UKISS at the final assessment (12–14 months) and over the telephone using a structured questionnaire by the VABS assessors (at 18 months) in ICISS.

2.2. Adverse events occurring during the first 42 days are reported

2.2.1. Statistical analysis

All analyses were done by intention to treat. The exposure variables were prednisolone or tetracosactide depot. Other explanatory variables included in the analyses were underlying aetiology and lead time as these have been shown to affect developmental outcome and spasm control. Chi square was used for simple comparisons of proportions, t tests for comparison of means and logistic regression or linear regression for multivariable analysis using STATA IC 11.2 (Statacorp, College Station, TX, USA).

2.2.2. Role of funding sources and ethics

Both trials were sponsored by the Royal United Hospital Bath NHS

Foundation Trust and have been previously published [7–10]. The funding sources had no involvement in study design, collection, analysis, interpretation, writing or the decision to submit for publication. We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. The appropriate research ethics bodies approved the trials and written informed consent was obtained.

3. Results

Fig. 1 shows the flow diagram for the combined studies. 55 infants in UKISS (30 prednisolone and 25 tetracosactide depot) and 71 in ICISS (34 prednisolone and 37 tetracosactide depot) were randomly allocated a hormonal treatment alone. Numbers and response by trial are shown in Table 1. In UKISS two infants received prednisolone instead of tetracosactide depot when the latter was unavailable due to supply shortages. Within ICISS, three infants allocated to tetracosactide depot alone received non-depot tetracosactide. There were no deaths in the first 42 days.

Important baseline characteristics are shown in Table 2. Both studies were parallel group, open label studies with concealed allocation of randomised treatments. The cessation of spasms outcomes were not blinded. The EEG outcomes were not blinded to treatment allocation in UKISS but were in ICISS.

Table 1
The day 13–14 cessation of spasms responses by trial and by treatment allocation.

	UKISS		ICISS	
	Total	Responders	Total	Responders
Prednisolone	30	21 (70%)	34	22 (65%)
Tetracosactide depot	25	19 (76%)	37	28 (76%)
Total	55	40 (73%)	71	50 (70%)

3.1. Cessation of spasms

The Day 13–14 outcome (Table 3, section A): this outcome was available in all 126 infants. For those on tetracosactide depot, 47 of 62 (76%) were free of spasms compared to 43 of 64 (67%) on prednisolone (difference 9%, 95% CI -7·2% to +25·2%, chi square 1·15, p = 0·28). Aetiology was not known in 1 and lead time not known in four infants. When aetiology and lead time (five categories) are taken into account, 121 results are available. In the multivariable analysis, tetracosactide depot was not significantly superior to prednisolone (Odds ratio 1·61, 95% CI 0·70-3·72, p = 0·26), when adjusting for underlying aetiology and lead-time to treatment. In this model, the presence of an underlying aetiology (Odds ratio 0·76, 95%CI 0·33-1·74, p = 0·51) and longer lead time was not significantly associated with spasms cessation at Day 13–14.

The Day 14–42 outcome (Table 3, section B): this outcome was available in 123 infants (clinical outcome not known in 3). For those on

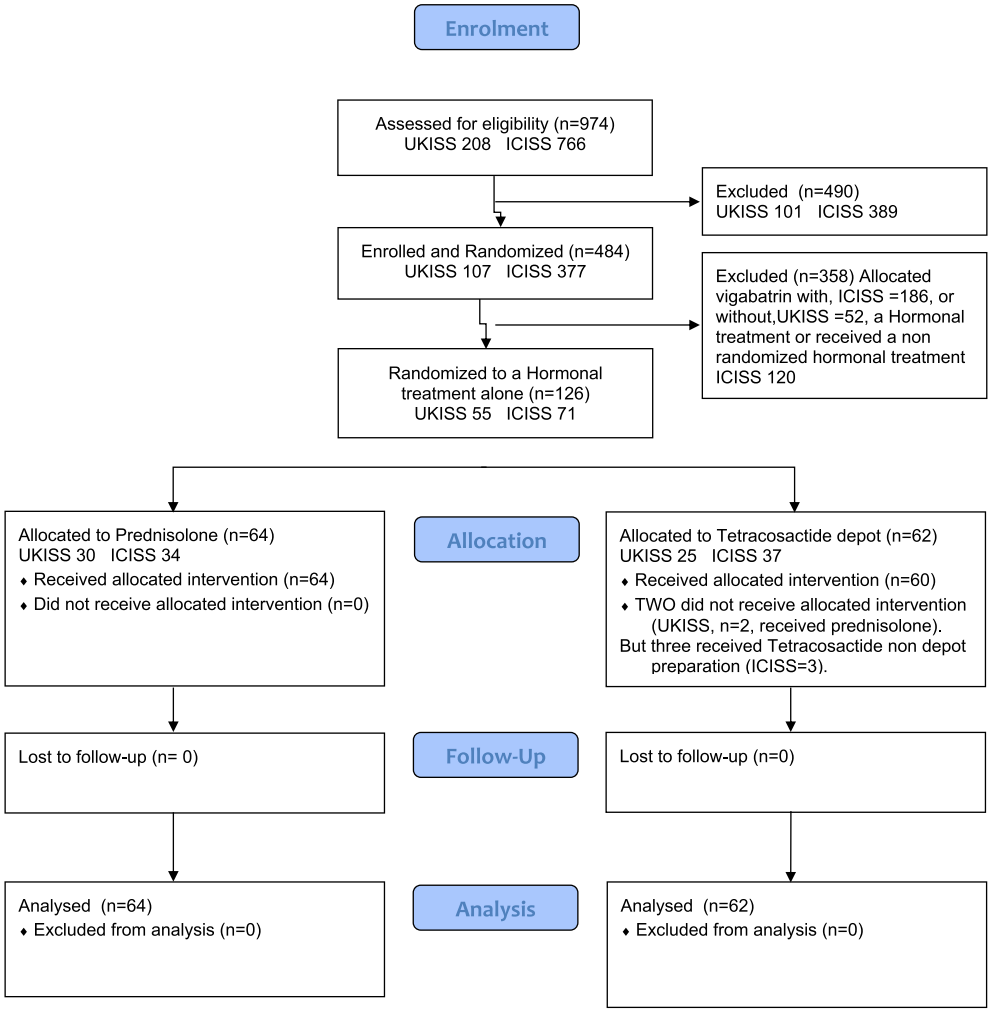

Fig. 1. Consort flow diagram combined trial profiles.

Table 2
Baseline characteristics for infants in each trial.

	UKISS	ICISS
Numbers	55	71
Age at trial entry		
Range in months	2–11	3–12
Median	6	7
AETIOLOGY		
Proven	29 (53%)	36 (51%)
None identified	25 (45%)	35 (49%)
Not known	1	0
LEAD TIME		
7 days or less	10	15
8–14 days	11	14
15 days to 1 month	5	18
1–2 months	9	15
>2 months	16	9
Not known	4	0

Table 3
Multivariable logistic regressions investigating the relationship between treatment type, presence of underlying aetiology and lead-time to treatment and the trial clinical and electroclinical outcomes.

A
Day 13–14 outcome

	Adjusted Odds Ratio	95% CI	p
Treatment	1.61	0.70–3.72	0.26
Aetiology	0.76	0.33–1.74	0.51
8–14 Days	0.54	0.15–1.98	0.35
14–28 Days	0.60	0.16–2.27	0.45
1–2 Months	1.17	0.27–5.08	0.84
>2 Months	0.44	0.12–1.60	0.21

B
Day 14–42 outcome

	Adjusted Odds Ratio	95% CI	p
Treatment	1.58	0.73–3.44	0.25
Aetiology	0.99	0.95–1.04	0.76
8–14 Days	0.37	0.11–1.22	0.10
14–28 Days	0.66	0.19–2.23	0.50
1–2 months	0.93	0.26–3.26	0.90
>2 months	0.68	0.20–2.33	0.54

C
Day 13–14 electroclinical outcome

	Adjusted Odds Ratio	95% CI	p
Treatment	1.70	0.74–3.90	0.21
Aetiology	0.80	0.35–1.83	0.60
8–14 Days	0.48	0.13–1.78	0.27
14–28 Days	0.64	0.17–2.48	0.52
1–2 Months	0.84	0.20–3.51	0.81
>2 months	0.43	0.11–1.59	0.20

D
Day 14–42 electroclinical outcome

	Adjusted Odds Ratio	95% CI	p
Treatment	1.65	0.76–3.61	0.21
Aetiology	0.99	0.95–1.04	0.78
8–14 Days	0.34	0.10–1.14	0.08
14–28 Days	0.62	0.18–2.12	0.45
1–2 Months	0.67	0.19–2.34	0.53
>2 Months	0.58	0.17–2.00	0.39

The lead time comparisons are between the lead time stated and the shortest lead time, less than 7 days. Parameters of the logistic regression model: clinical response (1 = response, 0 = no response) or electro-clinical response (1 = response, 0 = no response); Treatment modality (1 = Tetracosactide depot, 0 = Prednisolone); aetiology (1 = known, 0 = not identified); Lead time (1 = 7 days or less, 2 = 8–14 days, 3 = 15 days to one month, 4 = one to two months, 5 greater than two months).

tetracosactide depot, 41 of 61 (67%) were free of spasms compared to 35 of 62 (56%) on prednisolone (difference 11%, 95% CI -6·4% to +28·4%, chi square 1·51, p = 0·22). When aetiology and lead time are taken into account (aetiology not known in 1, lead time not known in 3) 119 results were available. Tetracosatide depot was not significantly superior to prednisolone (Odds ratio 1·58, 95%CI 0·73-3·44, p = 0·25). The presence of an underlying aetiology (Odds ratio 0·99, 95%CI 0·95-1·04, p = 0·76) and longer lead times to treatment were not significantly associated with spasm cessation.

The day 13–14 electroclinical outcome (Table 3, section C): This was available in 117 infants (EEG not known in 9). For those on tetracosactide depot, 42 of 58 (72%) were free of spasms compared to 37 of 59 (63%) on prednisolone (difference 9%, 95% CI – 8·3% to +26·3%, chi square 1·26, p = 0·26). When aetiology and lead time (aetiology not known in 1, lead time not known in 4) are taken into account, 112 results are available. Tetracosactide depot was not significantly superior to prednisolone (Odds ratio 1·70, 95%CI 0·74-3·90 p = 0·21), and the presence of an underlying aetiology (Odds ratio 0·80, 95%CI 0·35-1·83, p = 0·60) and longer lead-times were also not significantly associated with the electroclinical outcome.

The day 14–42 electroclinical outcome (Table 3, section D): This was available in 117 infants (clinical outcome not known in 3 and EEG not known in a further 6). For those on tetracosactide depot, 37 of 57 (65%) responded compared to 32 of 60 (53%) on prednisolone (difference 12%, 95% CI -6·4% to 30·4%, chi square 1·62, p = 0·20). When aetiology and lead time (aetiology not known in 1, lead time not known in 3) are taken into account, 113 results are available. Tetracosactide depot was not significantly superior to prednisolone (Odds ratio 1·65, 95%CI 0·76-3·61, p = 0·21). The presence of an underlying aetiology (Odds ratio 0·99, 95%CI 0·95-1·04, p = 0·78) and longer lead times were also not significantly associated with the electro-clinical outcome.

3.2. Developmental outcome

The VABS was completed in 121 infants. The results are shown in Table 4, section A, by treatment and aetiological category. The mean VABS score was 76·4 (95%CI: 72·9–79·8, range 44–138) for the whole cohort. There was no significant difference in mean VABS score of the 60 infants who received prednisolone compared with the 61 infants who received tetracosactide depot (74·8 (SD 18·3) versus 78·0 (SD 20·2) t = −0·91 p = 0·36). A multivariable analysis including type of treatment, presence of underlying aetiology and lead time as explanatory variables was performed. Aetiology status was not known in 1 and lead-time unknown in 3, therefore 117 infants were included in this analysis (see Table 4, section B). Type of treatment was not significantly associated with VABS score when adjusting for aetiology and lead-time (Coef 1·97 [95%CI -4·35 to 8·30], p = 0·54). However, the presence of an underlying aetiology was associated with a significant fall in VABS score (Coef −17·81 [95%CI -24·08 to −11·54], p < 0·001). Similarly, longer lead-times to treatment result in a fall in VABS score with a significant difference between the longest lead-time group (>2 months) and shortest lead time groups (<7 days), (Coef −10·98 [95% CI -20·80 to −1·16] p = 0·03).

Mutivariable models were also constructed including ongoing infantile spasms and ongoing epilepsy of any type as explanatory variables (Table 4, sections C and D). Again, in these models, the type of treatment did not significantly affect VABS score but the presence of an underlying aetiology and ongoing epilepsy (either spasms or epilepsy of any type) were independently significantly associated with large decrements in VABS score.

3.3. Epilepsy outcome

The epilepsy status at the time of developmental assessment (14 months for participants in UKISS, and 18 months for participants in ICISS) was known in 124 infants (Table 5), sub-divided by treatment

Table 4
Vineland adaptive behaviour scale scores.

A		Mean VABS and 95% CI	
	NUMBERS	Prednisolone	Tetracosactide depot
No identified aetiology			
UKISS	24	85.2 (72.6–97.8)	91.2 (81.8–100.5)
ICISS	35	83.2 (72.5–93.9)	84.4 (74.8–94.0)
COMBINED	59	84 (76.4–91.6)	87.1 (80.5–93.7)
Proven Aetiology			
UKISS	27	72.3 (67.5–77.0)	69 (60.2–77.9)
ICISS	34	60.4 (54.9–65.9)	69.9 (59.0–80.8)
COMBINED	61	66.1 (62.1–70.2)	69.5 (62.5–76.6)
Aetiology not known			
UKISS	1		57
ICISS	0		
TOTALS	121	74.8 (70.0–79.5)	78.0 (72.8–83.1)

B
Multivariable linear regression with VABS score as outcome and type of treatment (Tetracosactide vs Prednisolone), presence of underlying aetiology and lead-time to treatment as explanatory variables

	Regression Coefficient	95% CI	P value
Treatment	1.97	−4.35 to 8.30	0.54
Aetiology	−17.8	−24.1to −11.5	<0.001
Lead Time:			
8–14 Days	1.22	−8.6 to 11.0	0.81
14–28 Days	−6.79	−16.8 to 3.2	0.18
1–2 Months	−3.76	−13.6 to 6.0	0.45
> 2 Months	−11.0	−20.8 to −1.2	0.029

C
Multivariable linear regression with VABS score as outcome and type of treatment (Tetracosactide vs Prednisolone), ongoing infantile spasms, presence of underlying aetiology and lead-time to treatment as explanatory variables

	Regression Coefficient	95% CI	P value
Treatment	3.50	−2.4 to 9.4	0.24
Aetiology	−16.27	−22.1 to −10.4	<0.001
Spasms	−17.94	−25.92 to −9.96	<0.001
8–14 Days	1.58	−7.4 to 10.6	0.73
14–28 Days	−8.41	−17.7 to 0.8	0.07
1–2 Months	−6.45	−15.6 to 2.7	0.17
>2 Months	−6.95	−16.2 to 2.3	0.14

D
Multivariable linear regression with VABS score as outcome and type of treatment (Tetracosactide vs Prednisolone), ongoing epilepsy (any type), presence of underlying aetiology and lead-time to treatment as explanatory variables

	Regression Coefficient	95% CI	P value
Treatment	1.39	−4.4 to 7.2	0.64
Aetiology	−13.43	−19.4 to −7.4	<0.001
Epilepsy	−16.00	−22.7 to −9.34	<0.001
8–14 Days	0.54	−8.4 to 9.5	0.91
14–28 Days	−8.58	−17.7 to 0.6	0.07
1–2 Months	−4.67	−13.6 to 4.3	0.30
>2 Months	−5.52	−14.8 to 3.7	0.24

[1]Mean VABS score for the whole cohort was 76.4 (95% CI: 72.9–79.8, range 44–138).
[2]VABS score was not known in 5.

modality, presence of underlying aetiology or not, and the relevant trial (UKISS or ICISS). The proportion of patients with ongoing infantile spasms at this stage was virtually identical (19% and 20%) in the two treatment groups. The proportion with ongoing epilepsy of any type was 20 of 61 (33%) in the ACTH group compared with 26 out of 63 (41%) in the prednisolone group (difference 8%, 95% CI -9·2% to +25·2%, Chi^2 0·95, p = 0·33). There was a significant difference between the number of patients with ongoing epilepsy (both treatments grouped together) at final assessment in the UKISS trial 27 out of 55 (49%) compared with 19 out of 69(28%) in the ICISS trial (difference 21%, 95% CI + 3·7% to +38·3%, Chi^2 6·7, p = 0·01).

3.4. Adverse events

There were no deaths due to a trial treatment. Two infants, both in UKISS, had treatment withdrawn due to an adverse event, one allocated prednisolone and one tetracosactide depot. The individual adverse reactions (Table 6) show very similar profiles for each treatment group.

4. Discussion

The strength of this analysis is the relatively large number of infants studied, the use of individual patient data and the prospective nature of the analysis from the same trial team using many of the same procedures. Trials are difficult to do in paediatrics and obtaining additional information through secondary randomisations is an ethically sound approach. However, secondary analyses may be under-powered because the trial sample size will be determined by the primary outcome comparison. In addition, in ICISS we did not know how many parents would wish to choose their infant's hormonal treatment. Acknowledging that the power of our analysis to detect a small but clinically significant difference was limited, we did not find evidence of a significant difference between the two treatment modalities in cessation of spasms.

The inclusion in this analysis of only those patients who were randomised to a hormonal treatment will hopefully reduce the risk of bias. However, we have to acknowledge that it is possible some hidden selection bias could be introduced from the ICISS data because we do not know if there were any systematic factors that might be related to outcome which influenced whether parents allowed their children to be randomised to a hormonal modality or whether they insisted on exercising parental choice.

The cessation of spasms outcome for a full 4 week period from Day 14–42 is now the more rigorous and preferred outcome in treatment trials of infantile spasms, having been recommended by the West Delphi group [11]. However, we chose the Day 13–14 outcome as the main outcome in this analysis since it was collected prospectively in both trials and was known in all infants. We also looked at both the Day 14–42 outcome and the electroclinical outcome, a more rigorous measure of response to treatment, and still did not find a significant treatment difference. The presence of an underlying aetiology and longer lead time to treatment were not shown to be significant predictors of cessation of spasms in this analysis but they were strongly associated with developmental outcome, in line with our previous analyses of UKISS and ICISS where we showed that underlying aetiology and lead time have a greater effect on developmental outcome than on control of spasms. Lead time requires large numbers of infants to be analysed to see an effect on control of spasms.

Neither long term epilepsy (including infantile spasms) nor developmental outcome was associated with initial trial treatment. Earlier control of spasms is believed to result in better developmental outcome [6,7,10] and this data support that conclusion when comparing a long lead time to a short lead time. Longer-term epilepsy outcome was better in the infants in ICISS but the later age of assessment in ICISS compared to UKISS and the different methodologies used mean that caution should be exercised in interpreting this finding. Infantile spasms tend to resolve with increasing age. However, the lead-times to treatment in the ICISS study were markedly shorter than those in the UKISS study and general standards of care may have improved over time leading to better long-term epilepsy outcomes.

Although adverse reactions might influence choice of treatment, we found no deaths and few adverse reactions causing cessation of treatment. Neither was there any evidence of a meaningful difference between prednisolone and tetracosactide depot in the number of adverse reactions.

The presence of both any epilepsy and of spasms at the time of developmental assessment was shown to be associated with a substantial lowering of developmental outcome despite controlling for the presence or absence of an underlying aetiology. It may be that the continuing

Table 5
The number of infants with epilepsy (any type) or infantile spasms at final assessment are shown here by aetiologic group, treatment modality and trial (UKISS or ICISS).

		Any Epilepsy		Any Spasms	
	NUMBERS	Prednisolone	Tetracosactide depot	Prednisolone	Tetracosactide depot
No identified aetiology					
UKISS	25	4 of 13 (31%)	3 of 12 (25%)	3 of 13 (23%)	2 of 12 (17%)
ICISS	35	5 of 17 (29%)	3 of 18 (17%)	2 of 17 (12%)	2 of 18 (11%)
Proven Aetiology					
UKISS	29	10 of 17 (59%)	9 of 12 (75%)	4 of 17 (24%)	5 of 12 (42%)
ICISS	34	7 of 16 (44%)	4 of 18 (22%)	3 of 16 (19%)	3 of 18 (17%)
Aetiology not known					
UKISS	1		1		0
ICISS					
Total					
UKISS	55	14 of 30 (47%)	13 of 25 (52%)	7 of 30 (23%)	7 of 25 (28%)
ICISS	69	12 of 33 (36%)	7 of 36 (19%)	5 of 33 (15%)	5 of 36 (14%)
Combined Totals	124	26 of 63 (41%)	20 of 61 (33%)	12 of 63 (19%)	12 of 61 (20%)

Table 6
Adverse reactions.

	Prednisolone									Tetracosactide Depot								
	UKISS	%	SAR	ICISS	%	SAR	Total	%	SAR	UKISS	%	SAR	ICISS	%	SAR	Total	%	SAR
Total study number of infants	**30**			**34**			**64**			**25**			**37**			**62**		
Specific Adverse Reactions																		
Allergic rash or anaphylaxis	0			0		0	0	0	0	0	0		1	3	0	1	2	0
Dermatological	1	3		0	0	0	1	2	0	3	12		0	0	0	3	5	0
Drowsiness	7	23		1	3	0	8	13	0	3	12		0	0	0	3	5	0
Endocrine/Metabolic Disturbance	0	0		0	0	0	0	0	0	0	0		0	0	0	0	0	0
Fluid/Electrolyte disturbance	4	13	**1**	3	9	0	7	11	**1**	2	8		7	19	**2**	9	15	**2**
Gastro-intestinal upset	9	30		6	18	0	15	23	0	5	20		4	11	**1**	9	15	**1**
Hypertonia	0	0		2	6	0	2	3	0	2	8		4	11	0	6	10	0
Hypotonia	0	0		1	3	0	1	2	0	0	0		0	0	0	0	0	0
Immunosuppression	0	0		1	3	**1**	1	2	**1**	0	0		0	0	0	0	0	0
Increased appetite	4	13		8	24	0	12	19	0	3	12		9	24	0	12	19	0
Infection	5	17		3	9	**1**	8	13	**1**	0	0		4	11	0	4	6	0
Irritability	13	43		9	26	0	22	34	0	7	28		15	41	**1**	22	35	**1**
Neuropsychiatric	2	7		3	9	0	5	8	0	0	0		6	16	0	6	10	0
Varicella zoster (chicken pox)	1	3		1	3	0	2	3	0	1	4		0	0	0	1	2	0
Weight gain	0	0		6	18	0	6	9	0	0	0		7	19	0	7	11	0
(U) Sweating	0	0		0	0	0	0	0	0	0	0		1	3	0	1	2	0
Other	4	13		0	0	0	4	6	0	5	20		0	0	0	5	8	0

seizures do harm through an uncontrolled developmental epileptic encephalopathy although a significant contribution from underlying aetiologies for which we cannot control might also have an effect. Such aetiologies might cause both poor development and continuing epilepsy. However, the possibility of a continuing developmental epileptic encephalopathy and the frequency of seizures suggest that methods to better control the epilepsies are still required.

The previously reported results from ICISS suggest that combined treatment with vigabatrin and a hormonal treatment from day one was better for control of spasms [8] than a hormonal treatment alone. Any difference between prednisolone and tetracosactide depot given alone may not apply to infants who also receive vigabatrin from day one in combination treatment, as we have not studied combination treatment in this analysis. However, it is worth noting that a previous analysis of all the data in the ICISS trial that included patients on both combination therapy and hormonal therapy alone and patients who had been randomised to their hormonal therapy as well as those who had their hormonal therapy determined by parental choice, has shown that patients receiving tetracosactide were more likely to achieve an electroclinical response than those receiving prednisolone [8]. In ICISS, developmental outcome did not differ significantly between the combination treatment and hormonal treatment alone groups, perhaps because of the rapid cross over to include vigabatrin in those who had only been allocated a hormonal treatment [10]. Some infants will not be able to receive vigabatrin – perhaps because of cost, availability or a pre-existing visual disorder - and the results of this analysis suggest that either prednisolone or tetracosactide depot could be offered.

We do not know exactly how either prednisolone or tetracosactide works. One theory suggests that reducing ARH (adrenocorticotrophic releasing hormone) reduces the risk of seizures and thus ACTH or tetracosactide depot should be used [12]. In the countries recruiting into UKISS and ICISS (UK, Australia, Germany, New Zealand, Switzerland), there does not appear to be a significant difference in effectiveness between prednisolone and tetracosactide depot. Gowda et al. have similarly shown that there does not appear to be a difference in effectiveness between ACTH and prednisolone in the treatment of IESS in a randomized study in India but the sample size was very small (n = 33) and it is not clear from their paper which form of ACTH was being used [13]. Sanchez-Fernandez et al. have recently published a systematic review, meta-analysis and cost-effectiveness study looking at comparisons of high dose prednisolone versus ACTH in the treatment of IESS [14]. Their main findings are that there appears to be no clear difference in effectiveness between ACTH and prednisolone but that prednisolone is considerably more cost-effective than ACTH. Sanchez-Fernandez et al. appear to make no distinction between the different forms of ACTH used in the studies included in their analysis but base their cost-effectiveness calculations on the cost of natural ACTH used in the USA. In Sri Lanka, a trial comparing prednisolone to Acton Prolongatum (an injectable

synthetic ACTH of short duration given on alternate days whereas tetracosactide depot has a prolonged action) showed that prednisolone was better at controlling spasms [15]. The difference between the results from UKISS and ICISS and the Sri Lankan study may relate to the difference in duration of action. In contrast to prednisolone, prednisone [16,17] is an inactive compound that has to be metabolized to prednisolone to have any therapeutic effect and infants have limited ability to do this [18]. We do not recommend its use. Until further information is available, we recommend using the preparations, dosages and durations of prednisolone and tetracosactide depot which were used in these studies. Given the absence of a significant difference between their effects in the treatment of IESS, it is pertinent to consider that, compared to tetracosactide depot, oral prednisolone is much cheaper, easier to store, can be administered without injections or frequent visits to health care providers and is universally available.

Statement

The authors affirm that the work described is consistent with the journal's guidelines for ethical publication.

Declaration of competing interest

JPO unsuccessfully approached Aventis for funding of a follow up study to look at visual field defects: he appeared in a promotional video for Aventis: he received income from UCB Pharma. The study sponsor for UKISS and ICISS received funding from Marathon and from UCB Pharma which was used in part to fund the research reported including salaries to JPO and SE. JPO, SE, FJKOC, EH and AL all received IP payments from the sponsor relating to funding from Marathon. AL received funding from Hoechst-Marion-Roussel to attend a conference. No other authors declared a conflict of interest.

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References

[1] P. Pavone, P. Striano, R. Falsaperla, et al., Infantile spasms syndrome, West syndrome and related phenotypes: what we know in 2013, Brain Dev. 36 (2014) 739–751.
[2] I.E. Scheffer, S. Berkovic, G. Capovilla, et al., ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology, Epilepsia 58 (2017) 512–521.
[3] E.C. Hancock, J.P. Osborne, S.W. Edwards, Treatment of infantile spasms, Cochrane Database Syst. Rev. 6 (2013), CD001770.
[4] J. Engel Jr., International League Against Epilepsy, A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: report of the ILAE Task Force on Classification and Terminology, Epilepsia 42 (2001) 796–803.
[5] R. Riikonen, Epidemiological data of West syndrome in Finland, Brain Dev. 23 (2001) 539–541.
[6] F.J. O'Callaghan, A.L. Lux, K. Darke, et al., The effect of lead time to treatment and of age of onset on developmental outcome at 4 years in infantile spasms: evidence from the United Kingdom Infantile Spasms Study, Epilepsia 52 (2011) 1359–1364.
[7] A.L. Lux, S.W. Edwards, E. Hancock, et al., The United Kingdom Infantile Spasms Study (UKISS) comparing hormone treatment with vigabatrin on developmental and epilepsy outcomes to age 14 months: a multicentre randomised trial, Lancet Neurol. 4 (2005) 712–717.
[8] F.J. O'Callaghan, S.W. Edwards, F.D. Alber, et al., Safety and effectiveness of hormonal treatment versus hormonal treatment with vigabatrin for infantile spasms (ICISS): a randomised, multicentre, open-label trial, Lancet Neurol. 16 (2017) 33–42.
[9] A.L. Lux, S.W. Edwards, E. Hancock, et al., The United Kingdom Infantile Spasms Study comparing vigabatrin with prednisolone or Tetracosactide at 14 days: a multicentre, randomised controlled trial, Lancet 364 (2004) 1773–1778.
[10] F.J.K. O'Callaghan, S.W. Edwards, F.D. Alber, et al., Vigabatrin with hormonal treatment versus hormonal treatment alone (ICISS) for infantile spasms: 18-month outcomes of an open-label, randomised controlled trial, Lancet Child Adolesc Health 2 (2018) 715–725.
[11] A. Lux, J.P. Osborne, A proposal for case definitions and outcome measures in studies of infantile spasms and West syndrome: consensus statement of the West Delphi group, Epilepsia 45 (2004) 1316–1428.
[12] K.L. Brunson, S. Avishai-Eliner, T.Z. Baram, ACTH treatment of infantile spasms: mechanisms of its effects in modulation of neuronal excitability, Int. Rev. Neurobiol. 49 (2002) 185–197.
[13] V.K. Gowda, V. Narayanaswamy, S.K. Shivappa, et al., Corticotrophin-ACTH in comparison to prednisolone in west syndrome – a randomized study, Indian J. Pediatr. 86 (2) (2019) 165–170.
[14] I. Sanchez Fernandez, M. Amengual-Gual, M. Gainza-Lein, et al., Cost-effectiveness of adrenocorticotropic hormone versus oral steroids for infantile spasms, Epilepsia 62 (2021) 347–357.
[15] J. Wanigasinghe, C. Arambepola, S.S. Ranganathan, S. Sumanasena, Randomised, single-blind, parallel clinical trial on efficacy of oral prednisolone versus intramuscular corticotropin on immediate and continued spasm control in West syndrome, Pediatr. Neurol. 53 (2015) 193–199.
[16] T.Z. Baram, W.G. Mitchell, A. Tournay, O. Carter-Snead, R.A. Hanson, E.J. Horton, High dose corticotropin (ACTH) versus prednisone for infantile spasms: a prospective, randomized, blinded study, Pediatrics 97 (1996) 375–379.
[17] R.A. Hrachovy, J.D. Frost, P. Kellaway, T.E. Zion, Double-blind study of ACTH versus prednisone therapy in infantile spasms, J. Pediatr. 103 (1983) 641–644.
[18] Honor J, Personal Communication.