Supplementary Online Material

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**Table S1.** Search Strategy for MEDLINE via PubMed (executed September 30, 2020)
**Table S2.** Overview of Studies Evaluating RCI and Synthetic ACTH Therapies Excluded from the Meta-analysis
**Table S3.** Jadad Score and Cochrane Risk of Bias Assessment of Included Trials

This supplementary material has been provided by the authors to give readers additional information about their work.
Table S1. Search Strategy for MEDLINE via PubMed (executed September 30, 2020)

| Line no. | Search term |
|----------|-------------|
| 1        | “Spasms, Infantile”[MeSH] OR “salaam spasm”* |
| 2        | “Adrenocorticotropic Hormone”[MeSH] OR “Cosyntropin”[MeSH] |
| 3        | “Acthar” OR “corticotropin”* |
| 4        | #1 AND (#2 OR #3) |
| 5        | Filters: |
|          | • Language: English |
|          | • Species: Humans |

Study design: Clinical Trial; Meta-Analysis; Pragmatic Clinical Trial; Randomized Controlled Trial; Systematic Reviews; Journal Article

Table S2. Overview of Studies Evaluating RCI and Synthetic ACTH Therapies Excluded from the Meta-analysis

| Author, Year, Location | Study Design | Population | Treatments (Regimen) | Key Findings | Reason for Exclusion |
|------------------------|--------------|------------|-----------------------|--------------|---------------------|
| **Studies Evaluating RCI** |              |            |                       |              |                     |
| Dressler et al, 2015 (Austria) | Prospective, Randomized cross-over, Single center | Cases with a confirmed diagnosis of West Syndrome based on EEG monitoring; no prior treatment; age=0-27 months | RCI: 150 IU/m², tapering over 28 days Keto diet | Cessation of spasms in 54% on RCI compared to 45% on keto diet. No significant difference | Clinical trial study with no common comparator arm for comparison with synthetic ACTH treatment; RCI compared to keto diet |
| Knupp et al, 2016 (US) | Prospective, Multicenter | New onset of IS; age = 2-24 months | RCI: 150 IU/m²/d, tapering to 10 IU/m²/d OCS: 40 mg/d, tapering to 10 mg/d | 55% infants on RCI showed clinical remission and resolution of hypsarrhythmia compared to 39% on OCS (P<0.001) | Observational prospective study design |
| Hrachovy et al, 1994 (US) | RCT, Single center | Newly diagnosed cases of IS with demonstrated hypsarrhythmia (EEG findings), cryptogenic or symptomatic group, not previously been treated with ACTH or OCS | High dose RCI: 150 U/m²/d Low dose RCI: 20 to 30 U/d | No significant difference between response rate, defined as cessation of spasms and disappearance of hypsarrhythmia (high dose: 50%, low dose: 58%) | Dose comparison clinical trial study |
| Snead et al, 1989 (US) | Prospective, Single center | Diagnosis of IS, made by clinical history and EEG; mean age = 43.3 months | RCI: 75 - 150 IU/m²/d | Cessation of spasms and resolution of hypsarrhythmia in 14 out of 15 children; 93.3% response | Observational prospective study design |
| Dreifuss et al, 1986 (US) | RCT, Multicenter | IS documented by a hypsarrhythmic or modified hypsarrhythmic pattern (EEG findings), no prior use of treatment with ACTH, OCS, or nitrazepam; mean age: 8.4 months | RCI: 40 IU/d Nitrazepam: 0.2 mg/kg/d in two or 1 mg twice daily | 75-100% reduction in spasm frequency was 57% for ACTH and 52% for nitrazepam. Both groups showed significant reduction in spasms from baseline. No significant difference between groups. | Clinical trial study with no common comparator arm for comparison with synthetic ACTH treatment; RCI compared to nitrazepam |
| Author, Year          | Study Design               | Population                                                                 | Treatments (Regimen)                                      | Key Findings                                                                                     | Reason for Exclusion                                      |
|----------------------|----------------------------|----------------------------------------------------------------------------|----------------------------------------------------------|--------------------------------------------------------------------------------------------------|----------------------------------------------------------|
| Lombroso et al, 1983 (US) | Prospective, Single center | Diagnosis of typical or atypical IS, presence of EEGs with hypsarrhythmia, presence of cryptogenic or symptomatic cases; age: <24 months | RCI: 110 units/m²/d OCS: 2 mg/kg/d | 48% and 43% patients on RCI achieved cessation of spasms and resolution of hypsarrhythmia compared to 38% and 35% on OCS, respectively | Observational prospective study design                   |
| Snead et al, 1983 (US)   | Prospective, Single center | Diagnosis of IS or other types of myoclonic seizures, or those with intractable seizures; mean age = 6.2 to 47.8 months | RCI: 75 - 150 IU/m³/d OCS: 3 mg/kg/d | Seizure control ranged from 67%-100% of the patients on RCI vs. 0%-59% on OCS. Resolution of hypsarrhythmia in 29/30 patients (96.7%) compared to 11/22 patients on OCS (50%) | Observational prospective study design                   |
| Singer, 1980 (US)         | Retrospective chart review, Single center | Seizure disorder characterized by massive myoclonic jerks, extensor spasms or a combination of the two, and an EEG pattern of hypsarrhythmia; modal age: 5 months | RCI: 80 IU every other day | Cessation of spasms in 74.5% with 5 to 6 months of RCI therapy (27/31 in early treatment group and 14/24 in late treatment group) | Single arm and observational retrospective study design |
| Studies Evaluating Synthetic ACTH₁⁻₂₄ (Tetracosactide, Synacthen) | | | | | |
| Jones et al, 2015 (Canada) | Retrospective case series review, Single center | Cases of newly diagnosed IS with demonstrated clinical spasms and hypsarrhythmia, cryptogenic or symptomatic IS; median age: 4 months | Tetracosactide: 1.9 mg/m² tapering to 0.06 mg/m² OCS: 4.5 mg/kg/d tapering to 1.5 mg/kg/d | Cessation of spasms and resolution of hypsarrhythmia in 80% children on synthetic ACTH₁⁻₂₄ vs. 20% on OCS | Observational retrospective study design |
| Ibrahim et al, 2010 (Pakistan) | Retrospective chart review, Single center | Diagnosed with IS, hypsarrhythmia on EEG and no diagnosis of tuberous sclerosis; no prior experience with vigabatrin, ACTH; mean age: 6.5 months | Tetracosactide: 40-80 IU daily Vigabatrin: 12.5–150 mg/kg/d | No statistically significant difference observed between 2 treatments (ACTH: 9/18 [50%]; vigabatrin: 21/38 [55.3%]) | Observational retrospective study design with no common comparator arm for comparison with RCI |
| Cohen-Sadan et al, 2009 (Israel) | Retrospective chart review, Multicenter | Patients with idiopathic West Syndrome; age: 2 to 9 months | Tetracosactide: 100 IU; alternate days Vigabatrin: 100–180 mg/kg/d | Cessation of spasms and resolution of hypsarrhythmia in 87% patients on synthetic ACTH₁⁻₂₄ compared to 78% on vigabatrin | Observational retrospective study design with no common comparator arm for comparison with RCI |
| Lin et al, 2006 (Taiwan) | Prospective, Multicenter | Diagnosis of West Syndrome or IS with hypsarrhythmia on EEG, never treated with ACTH or OCS; mean age: 8.2 months | Tetracosactide: 2.5 IU daily and tapered | 46/53 (86.8%) had cessation of spasms, of which 35/46 (76.1%) had complete cessation of spasms | Single arm with observational prospective study design |
Table S2. Overview of Studies Evaluating RCI and Synthetic ACTH Therapies Excluded from the Meta-analysis

| Author, Year          | Study Design          | Population                                                                 | Treatments (Regimen)                                      | Key Findings                                                                 | Reason for Exclusion               |
|-----------------------|-----------------------|----------------------------------------------------------------------------|-----------------------------------------------------------|-------------------------------------------------------------------------------|------------------------------------|
| Azam et al, 2005 (Pakistan) | Retrospective chart review, Single center | Characteristic seizures of IS, hypsarrhythmia on EEG, no previous experience with ACTH or OCS; mean age: 11 months | Tetracosactide: 20-40 IU OCS: 2-3 mg/kg/d | No significant difference between treatment groups: ACTH: 27/33 (82%) responded (11/33 [33.3%] remained spasms free); OCS: 51/72 (71%) responded (17/72 [24%] remained spasm-free) | Observational retrospective study design |
| Kurokawa et al, 1980 (Japan) | Cross-sectional survey, Multicenter | Children with West Syndrome or Lennox-Gastaut syndrome characterized by spasms starting in infancy; age: ≤6 years | Tetracosactide: 10-20 mg/d OCS: 10 mg/kg/d | Cessation of spasms in 75.6% patients on synthetic ACTH1-24 vs. 38.0% on OCS. Resolution of hypsarrhythmia in 33.5% of patients on synthetic ACTH1-24 vs. 20.4% on OCS. | Observational cross-sectional study design |

Studies Evaluating Synthetic ACTH1-39 (Corticotropin Carboxymethyl-cellulose, Acton Prolongatum)

| Author, Year          | Study Design          | Population                                                                 | Treatments (Regimen)                                      | Key Findings                                                                 | Reason for Exclusion               |
|-----------------------|-----------------------|----------------------------------------------------------------------------|-----------------------------------------------------------|-------------------------------------------------------------------------------|------------------------------------|
| Angappan et al, 2019 (India) | RCT, Single center | Newly diagnosed cases of West syndrome confirmed by clinical assessment and EEG, did not receive previous treatments with ACTH, OCS or zonisamide; median age: 8-10 years | Corticotropin carboxymethyl-cellulose: 30 IU/d to a maximum daily dose of 60 IU/d Zonisamide: 4-8 mg/kg/day to a maximum daily dosage of 25 mg/kg/day | Cessation of epileptic spasms was observed in 27% vs. 40% of patients on zonisamide and ACTH1-39, respectively. Resolution of hypsarrhythmia at 6 weeks was 36% vs. 71% for those on zonisamide and ACTH1-39, respectively. No significant difference between groups was observed. | Clinical trial study with no common comparator arm for comparison with synthetic RCI; Corticotropin carboxymethyl-cellulose compared to zonisamide |

Abbreviations: ACTH, adrenocorticotropic hormone; EEG, electroencephalogram; IS, infantile spasms; IU, international units; OCS, oral corticosteroids; RCI, repository corticotropin injection; RCT, randomized controlled trial; US, United States
Table S3. Jadad Score and Cochrane Risk of Bias Assessment of Included Trials

| Author, Year       | Randomization | Method of Randomization | Double-blind | Method of Double-blind | Withdrawals/Dropouts | Total Score |
|--------------------|---------------|-------------------------|--------------|------------------------|----------------------|-------------|
| Baram et al, 1996  | 1             | 1                       | 0            | 0                      | 1                    | 3           |
| Gowda et al, 2018  | 1             | 1                       | 0            | 0                      | 1                    | 3           |
| Hrachovy et al,    | 1             | 0                       | 1            | 0                      | 1                    | 3           |
| Lux et al, 2004    | 1             | 1                       | 0            | 0                      | 1                    | 3           |
| O’Callaghan et al, | 0             | 0                       | 0            | 0                      | 1                    | 1           |
| Wanigasinghe et al,| 1             | 1                       | 0            | 0                      | 1                    | 3           |

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