Seizure 59 (2018) 90–98

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Review

Epileptic spasms: Evidence for oral corticosteroids and implications for low and middle income countries

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ARTICLE INFO

Article history:
Received 26 March 2018
Received in revised form 7 May 2018
Accepted 11 May 2018
Available online xxx

Keywords:
Epileptic spasms
Oral corticosteroids
Prednisolone
Prednisone
Low and middle income countries (LMIC)

ABSTRACT

Implementation of international guidelines for the treatment of epileptic spasms, is challenging when access to adrenocorticotrophic hormone (ACTH) and vigabatrin is restricted, especially in Low and Middle Income Countries (LMIC). Oral corticosteroids are alternative interventions but evidence for the optimal agent, dose, duration, efficacy and long-term effects is lacking.

A systematic review of the literature was performed to assess the quality of evidence of prednisone and prednisolone (oral corticosteroids) for the management of epileptic spasms.

There is level C recommendation based on class III evidence to support the efficacy of oral corticosteroids for the acute clinical control of epileptic spasms and EEG resolution. Efficacy of oral corticosteroids in comparison to the internationally recommended intervention of ACTH has class IV evidence supporting level U recommendation. Similarly, there is no data on the risk of relapse with oral corticosteroids (class IV, level U), compared to ACTH. There is class IV evidence supporting level U recommendation for the safety of oral corticosteroids and class II evidence for level B recommendation for ACTH. In terms of oral corticosteroids and effects on long-term development there is class IV evidence leading to level U recommendation, compared to class III evidence supporting level C recommendation for ACTH.

Randomized controlled studies are needed to compare oral corticosteroids with ACTH, the optimal dosage and regimen as well as the long-term neurodevelopmental outcomes. Based on the limited existing studies a treatment guideline for LMIC is proposed which could be used to standardize interventions permitting clarification of these unmet questions.

1. Introduction

Access to hormonal and synthetic adrenocorticotrophic hormone (ACTH) is limited in many regions of the world [1]. This report explores the evidence to support use of oral corticosteroids, namely prednisolone or prednisone, in comparison to ACTH and other agents in the management of children with epileptic spasms.

The incidence of childhood epilepsy is highest in the infantile period and epileptic spasms are the most common seizure type in this age period [2].

Epileptic spasms are characterized by a brief contraction followed by a sustained tonic contraction of the neck, trunk, upper and lower legs and may be flexor, extensor or mixed [3]. They tend to occur in clusters, usually while awakening or just before sleep [4]. Spasms are frequently misdiagnosed with conditions such as colic, gastrooesophageal reflux and constipation, which results in delayed intervention [5]. The diagnosis of epileptic spasms is based on the semiology of the seizure and the interictal pattern of hypsarrhythmia on the EEG [6]. Hypsarrhythmia is defined as random high voltage slow waves accompanied by focal, multifocal or generalized spikes [7]. Variations from classic hypsarrhythmia are called modified hypsarrhythmia and may include focality, burst suppression, slow waves without spikes and partial preservation of the background [5].

The incidence of epileptic spasms in high income countries range between 0.25 and 0.42 per 1000 live births per year, peak onset is between 4 and 6 months, with a slight male preponderance [8]. The term “epileptic spasms” replaced “infantile spasms”, as the seizure type may persist or have the potential to develop beyond the infantile period [9].

The United Kingdom Infantile Spasms Study (UKISS) found that the most common aetiologies for ES were hypoxic ischaemic encephalopathy (10%), chromosomal (8%), cerebral malformations

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https://doi.org/10.1016/j.seizure.2018.05.008
1059-1311/

Table 1
Overview of the studies which included oral corticosteroids in the management of epileptic spasms.

Author, year Add country/ region	Study Design	Class	Sample Size	Treatment	Directness to study question	Consistency across studies	Efficacy	Outcomes Short Term	Long Term
Demarest et al 2017 USA [37]	Prospective, observational study, multicenter	Class II	447 total; 366 with hypsarrhythmia, 81 without hypsarrhythmia	196 ACTH 75IU/m^2 twice/day for 2 weeks followed by gradual tapering over 2 weeks, 85 prednisolone 10 mg 4 times daily for 2 weeks followed by weaning by 10 mg/ day every week, 66 vigabatrin 50–150 mg/kg/day divided into 2 doses	Yes	Yes	Prednisolone more effective than vigabatrin but less effective than ACTH in the treatment of epileptic spasms. Actual percentage response rate not given	Vigabatrin odds ratio (OR) 5.2, prednisolone OR 8, ACTH OR 10.2 cessation of spasms and resolution of hypsarrhythmia and no relapse within 3 months	
Yeh et al 2017 Korea [38]	Prospective open-label, uncontrolled, multicenter (2 tertiary hospitals)	Class III	14	Methylprednisone 30 mg/kg/day for 3 days followed by tapering doses of prednisolone 1 mg/kg 2 doses, rapidly reduced each week for 2–4 weeks	Yes	Consistent with doses compared to UKISS and Hussain et al, only sleep EEG's performed, follow up till 3 months	Yes, based on electroclinical response after 3 weeks. Overall response to steroids comparable to other studies	64.3% responded after 3 weeks with resolution of hypsarrythmia on EEG. Relapse rate for spasms 45.5%	55.5% remained seizure free after discontinuing steroids at 3 months. Developmental outcomes not assessed
Tang-Wai et al 2017 Canada [39]	Retrospective observational study, single center	Class III	26 IVIG vs 25 prednisone	IVIG 1 g/kg every 3 weeks and prednisone 2 mg/ kg/day (max 60 mg/day) for 2 weeks followed by 6–8 week taper OR prednisone 1–2 mg/kg/day (max 60 mg/day) for 2–4 weeks followed by 4–6 week taper	Yes	Only study comparing IVIG with prednisone. Only 1 other study (Bara, et al) with same dose of Prednisone. Follow up EEG's not consistent in IVIG group.	84.6% responded to IVIG, mean seizure reduction 77.3% after mean 9.8 weeks, 24% responded to prednisone with mean seizure reduction of 95%, 2.7 weeks mean time to max response	Percentage of seizure reduction higher for IVIG compared to prednisone ($p = 0.001$)	Long term and cognitive outcomes not assessed
O'Callaghan et al 2017 (ICISS) Australlia, Germany, New Zealand, Switzerland, UK [31]	Randomised, multi center, open label	Class I	186 vigabatrin and hormonal therapy vs. 191 on hormonal therapy	Vigabatrin (50–150 mg/kg/day) and hormonal treatment, 51 ACTH (40IU alternate days for 2 weeks), 134 prednisolone (10 mg 4 times/ day) for 2 weeks, tapered by 10 mg every 5 days vs. hormonal treatment (60 ACTH, 131 prednisolone)	Yes	Consistent with doses of prednisolone in Wanigasinghe et al, Ware et al, Mohamed et al and follow up. Parents allowed to choose type of hormonal therapy	Yes, hormonal treatment with vigabatrin significantly more effective at stopping spasms than hormonal therapy alone, similar to primary clinical response in UKISS BUT different definitions for "cessation of spasms".	Cessation of spasms in 89% on combination therapy vs. 69% on hormonal therapy ($p < 0.001$) on days 13 & 14, 19% relapsed by day 42 (33 on combination and 24 on hormonal treatment).	Day 14–42, no spasms in 72% combination therapy vs. 57% on hormonal therapy ($p = 0.002$). Electroclinical response 66% combination therapy vs. 55% hormonal therapy ($p = 0.023$).
Knupp et al 2016 USA [13]	Prospective, observational, multi center	Class II	230 total – ACTH 97, 54 prednisolone, 47 vigabatrin, 32 non-standard therapy	ACTH 75IU/m^2 twice/day for 2 weeks followed by gradual weaning over 2 weeks, prednisolone 10 mg 4 times daily for 2 weeks followed by weaning by 10 mg/ day every week, vigabatrin 50–150 mg/kg/day divided into 2 doses	Yes	Consistent with doses in ICISS, Ware et al, Mohammed et al and follow up in the short and long term. All patients received EEG's. Treatment not randomized, providers allowed to choose medication	ACTH associated with higher response rate than vigabatrin ($p = 0.038$) and oral corticosteroids (p-0.06)	After 2 weeks, 55% responded to ACTH, 39% to prednisolone, 36% to vigabatrin electroclinically. Relapse rate highest for oral corticosteroids, 24%.	After 3 months, sustained response to ACTH significantly higher than vigabatrin and marginally higher than oral corticosteroids. Long term developmental outcomes not assessed.