Seizure 47 (2017) 34–41

Contents lists available at ScienceDirect

Seizure

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

Breaking the cycle: A comparison between intravenous immunoglobulins and high dosage prednisone in the treatment of medically intractable epilepsy in children

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ARTICLE INFO

Article history:
Received 12 October 2016
Received in revised form 4 March 2017
Accepted 4 March 2017
Available online xxx

Keywords:
IVIG
Intravenous immunoglobulins
Prednisone
Corticosteroids
Intractable epilepsy
Pediatric epilepsy

ABSTRACT

Purpose: Because immune mediated mechanisms are suspected in epileptogenesis, IVIg and corticosteroids have been used as alternatives to treat refractory seizures. We present our experience treating intractable epileptic children with IVIg and prednisone.

Methods: Children with intractable epilepsy treated with prednisone or IVIg between 2005–2016 were reviewed retrospectively. Children with infantile spasms and autoimmune epilepsy were excluded. Data analyzed include epilepsy type and etiology, duration of epilepsy prior to treatment, seizure outcome, time to best seizure outcome, and adverse effects.

Results: Fifty-one patients were included: 26 received IVIg; 25 received prednisone. Etiologies were similar between cohorts: genetic (13 IVIg; 10 prednisone), lesional (8 IVIg; 7 prednisone), and unknown (5 IVIg; 8 prednisone). In the prednisone cohort, 92.0% had generalized epilepsy compared to 61.5% for IVIg.

Among the IVIg treated, 84.6% responded (10 genetic, 4 unknown, and 8 lesional) with mean seizure reduction of 77.3% and mean time to best response of 9.8 weeks. With prednisone, 24.0% responded (2 genetic, 3 unknown, and 1 lesional) with a mean seizure reduction of 95.0% and mean time to best response of 2.7 weeks. Adverse effects occurred in 2 and 16 patients treated with IVIg and prednisone, respectively. The difference in responders and seizure reduction was statistically significant ($p < 0.0001$ and $p = 0.001$, respectively).

Conclusion: IVIg had greater responders and lower adverse effects and honeymoon effect. This response was independent of epilepsy type, etiology, and duration suggesting different mechanisms of action between prednisone and IVIg and a common, reversible, immune-mediated pathway to intractability.

1. Introduction

Paediatric intractable epilepsy remains a problematic condition with high morbidity due to the high seizure burden and to the multiple antiepileptic medications (AEDs) used. Because AEDs share similar mechanisms of action aimed at affecting neuronal ion channels or neurotransmitter receptors, it is not surprising that the likelihood of additional AEDs resulting in significant seizure reduction is low. In addition, it is unclear if AEDs can modify the underlying process promoting seizures.

Neuroinflammation has been suspected to play a role in epileptogenesis and in the cycle of events leading to intractability. This notion is supported by animal models and by imaging and pathological studies in patients with intractable epilepsy [1–4]. With this hypothesis in mind, treatment with high dosage prednisone and intravenous immunoglobulins (IVIg) have been tried with the goal to break the cycle leading to refractory seizures [4] and to employ mechanisms that do not cause or compound the adverse effects of conventional AEDs.

To date, studies examining the use of IVIg and prednisone in epilepsy have been limited due to differences in treatment methodology and patient population [5–8]. Currently, there is no clear consensus of superiority or inferiority between these two

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http://dx.doi.org/10.1016/j.seizure.2017.03.004
1059-1311/

treatment options on seizure control. Furthermore, details on timing of response, duration of effect, relapse rate, and long term outcome are lacking.

In this study, a cohort of children treated with IVIg is compared to a cohort treated with high dosage prednisone. Etiology, outcome, the course of epilepsy during treatment, and adverse effects are among the factors examined.

2. Materials and methods

Patients were obtained from a pediatric epilepsy clinic (RTW) specializing in intractable pediatric epilepsy and serving northern Alberta, Saskatchewan, Yukon and Northwest Territories, and British Columbia. Patients under age 17 years who failed at least 2 AEDs and were treated with IVIg or prednisone from 2005 to 2016 and were included. Children with a clear or suspected immunological etiology for their epilepsy (e.g., Rasmussen's Encephalitis) or with infantile spasms and hypsarrhythmia were excluded. Children with a prior history of infantile spasms were included if they had a different type of epilepsy without hypsarrhythmia at the time of prednisone or IVIg. Of note, IVIg was initiated by RTW for all patients; however, prednisone was initiated by other neurologists in 7 patients.

IVIg was given monthly at 1 g/kg. Select patients underwent IVIg infusions every 3 weeks if seizures recurred or escalated by the week of their next infusion. IVIg was not given at intervals of less than 3 weeks. Repeated infusions were offered in patients who responded and relapsed. Prednisone initiated by RTW was prescribed at 2 mg/kg/day (maximum 60 mg/day) for 2 weeks followed by a 6–8 week taper. Prednisone initiated by other neurologists was prescribed at 1–2 mg/kg/day (maximum 60 mg/day) for 2–4 weeks followed by a 4–6 week taper. Repeated courses of prednisone were offered in patients who responded and relapsed. If patients did not respond to one treatment option, the other treatment option was offered.

Data was analyzed retrospectively and included sex, etiology of the epilepsy (lesional, unknown, genetic), age at time of first seizure, number of seizure types, baseline seizure frequency prior to treatment, number of AEDS tried, age at time of first IVIg or prednisone treatment, follow up time from first IVIg or prednisone treatment, best seizure response, time of first perceived seizure reduction, time of best seizure response, adverse effects, ability to reduce or discontinue AED's, response to subsequent courses of treatment, and EEG at time of best seizure response.

Because seizure frequency can vary in a given month, the baseline seizure frequency was defined as the average monthly seizure frequency that was sustained for a minimum period of 2 months prior to treatment and that was not due to an exacerbation from a transient condition. Responders to therapy were defined as having seizure reductions of at least 50% that persisted for a minimum period of 2 months. Best seizure response was defined as the maximum percentage of seizure reduction from baseline seizure frequency. Seizure frequencies were obtained from parental reports. These reports were compared to the seizure frequency reported by medical personnel in other clinical settings. Patients were excluded if there were significant inconsistencies in seizure reporting. A reduction in the spike frequency was defined as a 50% or greater reduction in spiking during comparable awake-sleep states on EEG before and after therapy.

Median values were used as a representation of the centre value because of the non-normal distribution of the data. The Mann-Whitney U test was therefore used to analyze the differences between the cohorts. Correlation between variables was determined by exploratory analysis of the scatterplot of the data and then by linear regression analysis.

3. Results

Fifty-one patients met the inclusion criteria: 26 patients received IVIg treatment, and 25 patients received high dose prednisone. The age at the time of the treatment initiation ranged from 2 to 13 years in the IVIg group, and from 18 months to 10 years in the prednisone group. One patient from the IVIg cohort was excluded due to unreliable reporting and non-compliance with medications.

Tables 1a and 1b show the characteristics of the patients of both cohorts and include the epilepsy etiology, type of epilepsy, duration of epilepsy until time of treatment with IVIg or high dose prednisone, and percent seizure reduction with treatment. Table 2 summarizes and compares the IVIg and prednisone cohorts. The mean age of seizure onset was 25.9 months in the IVIg group and 19.5 months in the steroid group. All children had tried multiple AEDs prior to the treatment initiation. Focal epilepsies accounted for 38.5% of the IVIg cohort and 8.0% of the prednisone cohort. The epilepsy etiologies were more evenly distributed between the cohorts. The mean duration of epilepsy prior to treatment was 1.3 fold higher in the IVIg cohort (60.3 months vs. 45.6 months). In total, 10 patients from the prednisone cohort subsequently underwent IVIg treatment due to poor response while only 1 patient from the IVIg was then treated with prednisone. For most patients who underwent treatment with prednisone before IVIg, there was an adequate wash out periods of greater than 1 year. Only patient #7 in the IVIg group (patient #10 in the prednisone cohort) received prednisone during the initial 6 months of IVIg because this patient's seizures had escalated and more aggressive therapy was required. The combination or prednisone and IVIg did not have any significant impact on this patient's seizures.

Within the IVIg cohort, 22 patients (84.6%) responded with a mean seizure reduction of 65.4% and a range of 0–100%. The mean seizure reduction among responders was 77.3%. The earliest time of first noted seizure reduction was 2 weeks after the first infusion with a mean time of 5.9 weeks. The mean time until best seizure reduction was 9.8 weeks after the first infusion (after the third infusion). Initial response followed by a sustained seizure relapse unaffected by at least 2 further IVIg infusions (honeymoon effect) was seen in 4 patients (2 unknown, 1 genetic, and 1 lesional). The majority of the genetic, unknown, and lesional epilepsies responded to IVIg. Of note, all children with lesional epilepsies had significant seizure reductions: all children with cortical dysplasia became seizure free and all children with lissencephaly had a 50% seizure reduction that was sustained. Epilepsy etiology, type, and duration prior to treatment did not appear to correlate with response. In total, 9 children in the IVIg cohort did not require any change to their AEDs, and AEDs were reduced in 8 children. Nine of the IVIg responders had reduced seizures that were sustained for periods ranging from 1–16 months (mean 6.6 months) after IVIg was discontinued. Patient #6 who had a response with the first course of IVIg relapsed and received an additional round of IVIg; however, with the second round of infusions, the first noted response occurred 24 weeks after monthly IVIg was restarted and the best response occurred at 28 weeks as opposed to 12 weeks and 20 weeks, respectively, with the first course of IVIg. Patient #1 had a recurrent seizure that was provoked by illness but no recurrent spontaneous seizures. The parents of all responders noted improved alertness, behaviour, and learning abilities.

In the prednisone cohort, 6 patients (24%) responded. There appeared to be an all or none type of response with a range of 70–100% seizure reduction with 5 achieving seizure freedom (mean seizure reduction of 95.0% among responders). Patients 6 and 19 remained seizure free for over 1 year after prednisone. Despite the