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Clinical and Neuro Electrophysiological Outcome of Intravenous Pulse Methylprednisolone Therapy in Children with Continuous Spike and Waves during Slow Sleep: A Self-Controlled Clinical Trial

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Abstract

Introduction: Continuous Spike-Wave during Slow Sleep (CSWS) is a complex epileptic encephalopathy in children characterized by seizures, neurocognitive decline, and Electrical Status Epilepticus during slow sleep (ESES). Despite its severe impact, there is a lack of consensus on effective treatment protocols. This study aimed to evaluate the efficacy of intravenous methylprednisolone (IV MP) pulse therapy in managing CSWS.

Methods: This single-center, self-controlled trial study was conducted involving 38 children diagnosed with CSWS at the Department of Neurology at BSMMU, Bangladesh, from June 2021 to May 2022. Participants underwent IV MP pulse therapy for five cycles, and their clinical seizure frequency, EEG outcomes, and psychological assessments were monitored and analyzed.

Result: Significant improvements were observed in clinical seizures, with 97.37% of participants showing improvement after the 5th cycle of IV MP pulse therapy. EEG outcomes also showed marked improvement, with a p-value of <0.001 indicating statistical significance. Psychological assessments revealed an improvement in cognitive function, further substantiating the therapy's efficacy.

Conclusion: The study demonstrates the promising potential of IV MP pulse therapy in treating CSWS, showing significant improvements in clinical seizures, EEG outcomes, and psychological status. Despite limitations like the single-center design and short study duration, these findings offer a valuable contribution to the existing literature and pave the way for future multi-center, randomized trials.

Keywords: Sleep disorders; Epileptic encephalopathy; iv methylprednisolone; ESES, CSWS

Introduction

Continuous Spike Wave during slow sleep is an childhood epileptic encephalopathy characterized by seizures, cognitive impairment, electrical status epilepticus in slow sleep [1]. Continuous Spike-Wave during Slow Sleep (CSWS) stands out as a particularly challenging and debilitating condition that has garnered increasing attention from the medical community [2,3]. This childhood epileptic encephalopathy evolves through four distinct stages: dormant (0 to 2 years), prodromal (2 to 4 years), acute (5 to 6 years), and residual (6 to 9 years). Each stage presents its own set of clinical challenges and requires specialized management [3]. Electrical Status Epilepticus

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during slow sleep (ESES) is a specific EEG pattern that is considered the hallmark of CSWS [2]. The prevalence of CSWS is a growing concern worldwide. Epidemiological studies have reported significant incidence and prevalence of CSWS emphasizing the need for complex health service and education planning [4]. In an outpatient pediatric series, 1 out of 440 (0.2%) epileptic children had CSWS. It indicate that not only the rarity but also its significant impact on the affected children and their families [5]. Review shows that typical age of onset is 4 to 7 and male to female ratio is 4:3 to 3:2 [3]. Treatment options for CSWS have evolved significantly over the years. While antiepileptic drugs (AEDs) have been the mainstay of treatment. Their efficacy varies widely and many children continue to experience poor outcomes including drug resistance [6]. Various studies and case reports have shown the promising response of steroids, particularly methylprednisolone, over the past two decades [7-9]. High-dose intravenous methylprednisolone pulse therapy has been found to have fewer side effects and maintain long-term efficacy compared to other forms of steroids [10,11]. The role of sleep in the management of CSWS is another area of active research. Sleep disorders are commonly observed in these children, affecting the quality of life and complicating treatment protocols [12]. The relationship between sleep and hormones like GH and Cortisol, cytokines like IL-6, and neurotransmitters has been established, and several antiepileptic drugs work by favoring REM sleep and reducing NREM sleep [13]. Genetic factors also play a crucial role in the onset and progression of CSWS. Advances in genomics have led to the identification of specific gene mutations that contribute to these conditions [14]. However, despite these advances, a significant proportion of CSWS remain idiopathic [15]. Due to the complexity and severity of CSWS in children comprehensive studies are needed that not only explore the underlying mechanisms but also evaluate the efficacy of existing and emerging treatment options. This study aims to fill this gap by investigating the clinical efficacy of pulse methylprednisolone therapy in children with CSWS, with a focus on seizure frequency, EEG status, and neuropsychological outcomes.

Methods

This study was a single-center, open-label self-controlled clinical trial conducted at the Department of Neurology, IPNA, BSMMU, Dhaka, Bangladesh, from June 2021 to May 2022. Ethical clearance was obtained from the Institutional Review Board of BSMMU. Written informed consent was secured from the parents or caregivers of all participating children. The study population consisted of children aged up to 15 years diagnosed with Continuous Spike-Wave during Slow Sleep (CSWS) based on clinical and EEG criteria. The sample size was calculated using a confidence level of 95% and a margin of error of 5%, resulting in a total of 24 participants. But we have to increase it to 38 to accommodate for lost to follow up missing values and to increase study power. Participants were recruited through outpatient clinics and were subjected to a comprehensive baseline evaluation, including a detailed medical history, neurological examination, EEG, neuroimaging. The primary outcome measures were seizure frequency, EEG status, and neuropsychological outcomes, assessed using standardized scales and tests. All participants received intravenous methylprednisolone pulse therapy according to a fixed protocol. One cycle of pulse therapy consisted of intravenous methylprednisolone administered at 30 mg/kg/day for five consecutive days, once a month. Each cycle was repeated for four consecutive months. Participants continued to receive their regular antiepileptic drugs (AEDs) at constant dosages throughout the study. Adverse effects were closely monitored and managed according to institutional protocols. Follow-up evaluations, including seizure, EEG were conducted after the completion of each treatment cycle and baseline neuropsychological score were compared with after 5th cycle therapy score. Therapeutic response assessed based on seizure frequencies recorded in seizure diaries prepared by the parents during follow-up in the epilepsy clinic as complete response (no seizure), no response of both frequent and infrequent seizure. Frequent seizure stated in the study as weekly, daily, or more frequent seizure. Infrequent seizure means fortnightly, monthly or more irregular and infrequent seizure. EEG was recorded by niccolite EEG machine before and within 7days after pulse therapy at 21 scalp electrodes according to the international 10-20 system at least 30 minutes duration in both awake and sleep state at EEG lab of IPNA. For clinical purpose, a nap EEG after sleep deprivation without sleep medication combined with an EEG during awake stage was recorded. The observation of EEG was by evaluating the background, frequency, presence of sleep marker, involved hemisphere, effect on photic stimulations & hyperventilation, calculated the percentage the spike & wave and classified as good and poor improvement where Good improvement =ESES status resolved that was spike wave index was 0% (grade-0) and spike wave index 0% -25% (grade-1), [2]. poor improvement = spike wave index 25-50% (grade-2),50-75% (grade-3), and >75% (grade-4). Baseline background and ESES pattern was compared with the value obtained at 5th cycle. Serial cognitive assessments were also performed using the age appropriate psychometric tools such as Bayley Scale for infant and Toddler Development (BSID) Third Edition - for children age < 42 months. Wechsler Preschool and Primary School of Intelligence (WPPSI) - Third UK edition –for the children age >42 months up to 7 years [5]. Wechsler Intelligence Scale for Children (WISC) – Fourth Edition for the children age > 7 years [5]. Subject were evaluated for the changes i.e. unchanged, improved or worsened of psychological assessment score. Data were collected using a pre-tested structured questionnaire.

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Data processing involved manual work initially, followed by coding and computerization. Statistical analysis was performed using SPSS-23 software. Categorical data were presented as frequency and percentage, while numerical data were presented as mean± SD. Pearson chi-square tests were used for categorical variables, and unpaired t-tests were used for normally distributed quantitative variables. Statistical significance was set at a p-value of <0.05.

Results

Table 1 displays the baseline characteristics of the participants. Most were aged 6-10 years (63.16%), followed by under 5 years (23.68%) and 10-15 years (13.16%). The mean age was 7.64 years with a standard deviation of 2.80. The sample was predominantly male (63.16%), with females at 36.84%. Regarding birth history, 34.21% had perinatal asphyxia (PNA), 10.53% were premature, and 5.26% had neonatal sepsis. Most were born at term (84.21%), with pre-term and post-term births at 13.16% and 2.63%, respectively. In terms of birth weight, 84.21% were appropriate for gestational age, and 15.79% were small for gestational age. The most common delivery method was Lower Uterine Cesarean Section (LUCS) at 44.74%, followed by normal vaginal delivery (NVD) at the hospital (28.95%) and at home (26.32%). Consanguinity was observed in 5.26% of the cases.

Table 1: Baseline characteristics distribution of the participants (N=38).

Variables	Frequency (n)	Percentage (%)
Age		
<5	9	0.2368
45571	24	0.6316
>10-15	5	0.1316
Mean ± SD	7.64 ± 2.80	
Gender		
Male	24	0.6316
Female	14	0.3684
Birth related history		
Perinatal Asphyxia	13	0.3421
Prematurity	4	0.1053
Neonatal sepsis	2	0.0526
No recorded history	19	0.5
Gestational age		
Pre term	5	0.1316
Term	32	0.8421
Post term	1	0.0263
Birth weight		
Appropriate for gestational age	32	0.8421
Small for gestational age	6	0.1579
Mode of delivery		
Normal vaginal delivery at home	10	0.2632
Normal vaginal delivery at hospital	11	0.2895
Lower Uterine Cesarean Section	17	0.4474
Consanguinity	2	0.0526

Table 2 shows the baseline seizure profile among the participants. The mean age of epilepsy onset was 4.56 years (SD 2.69), with a range from 0.25 to 15 years. The mean age for starting oral antiepileptic drugs was 4.63 years (SD 2.70), ranging from 0.5 to 15 years. Pulse therapy began at a mean age of 7.64 years (SD 2.80), with a range of 3 to 15 years. The lag period from seizure onset to pulse therapy initiation had a mean of 3.07 years (SD 1.94), ranging from 0.1 to 8.5 years. Focal seizures during sleep were the most common (89.47%). Generalized Tonic-Clonic Seizures (GTCS) occurred in 13.16%, focal to generalized seizures in 5.26%, absence seizures in 2.63%, and Status Epilepticus in 13.16%. Weekly seizures were the most frequent (36.84%), followed by daily or more frequent seizures (26.32%). Monthly seizures occurred in 7.89%, fortnightly in 10.53%, and irregular and infrequent in 15.79%. Nonclinical seizures were observed in 2.63%. A family history of epilepsy was present in 15.79% of participants.

Table 2: Baseline seizure profile of the study participant (N=38).

Variables	Mean ± SD	Min – max
Age(years)		
Age of onset of epilepsy	4.56 ± 2.69	0.25 – 15
Age of onset of oral antiepileptic drug	4.63 ± 2.70	0.5 – 15
Age of Pulse therapy	7.64 ± 2.80	3 – 15
Lag period(seizure onset to pulse therapy)	3.07 ± 1.94	0.1 – 8.5
Type of seizure		
	Frequency (n)	**Percentage (%)**
Generalized Tonic-Clonic Seizures	5	0.1316
Absence	1	0.0263
Focal seizure in sleep	34	0.8947
Focal to generalized	2	0.0526
Status Epilepticus	5	0.1316
Seizure frequency		
Weekly	14	0.3684
Daily or more frequently	10	0.2632
Monthly	3	0.0789
Fortnightly	4	0.1053
Irregular and infrequent	6	0.1579
Nonclinical seizure	1	0.0263
Family history of epilepsy	6	0.1579

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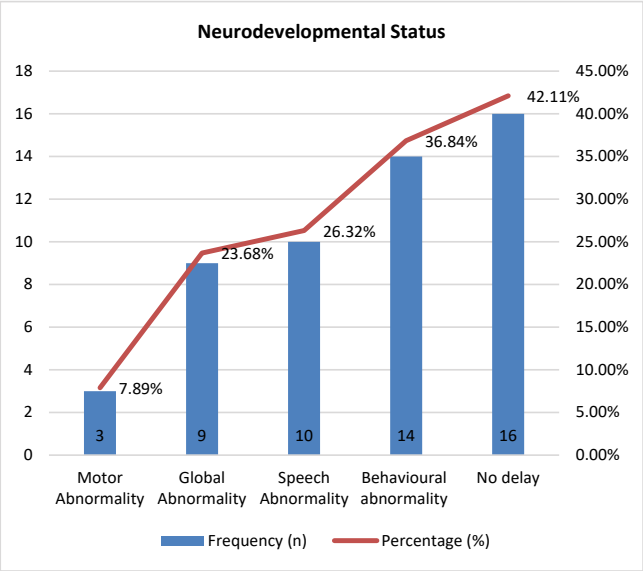
Figure 1 shows the distribution of various neurodevelopmental factors at baseline. Behavioral abnormalities were the most prevalent (36.84%), followed by speech abnormalities (26.32%), and global abnormalities (23.68%). Motor abnormalities were the least common (7.89%). Notably, 42.11% of the participants showed no developmental delay, indicating a varied neurodevelopmental profile among the participants.



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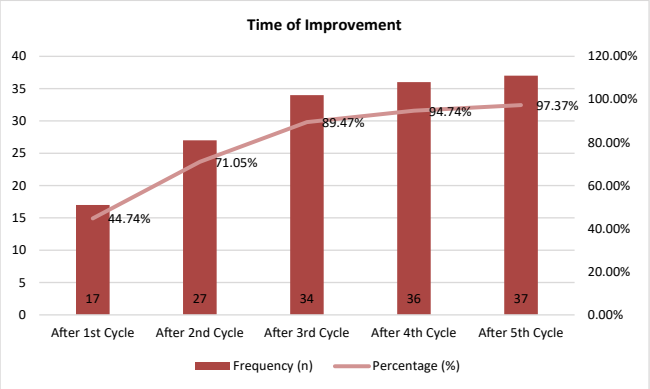

Figure 2: Pattern of Improvement of clinical seizure during different stages of pulse therapy.

Figure 2 illustrates the improvement in clinical seizures at different stages of pulse therapy. After the first cycle, 44.74% showed improvement. This increased to 71.05% after the second cycle, 89.47% after the third cycle, and 94.74% after the fourth cycle. By the end of the fifth cycle, 97.37% of participants showed improvement, demonstrating the effectiveness of the pulse therapy regimen.

Table 3 compares clinical seizure frequency before and after the fifth cycle of pulse therapy. For frequent seizures, the mean frequency per month decreased significantly from 111.89 ± 311.36 to 0.02 ± 0.08 ($p < 0.001$). For infrequent seizures, the mean frequency per month reduced from 12.10 ± 39.71 to 0.71 ± 2.67 ($p < 0.001$).

Table 4 presents the clinical and neuro-electrophysiological outcomes after the fifth cycle of IV Methylprednisolone (MP) pulse therapy. For frequent seizures, the mean score decreased from 81.11 ± 12.90 to 28.71 ± 28.68 ($p < 0.001$). For infrequent seizures, the mean score dropped from 71.93 ± 14.50 to 24.00 ± 24.50 ($p < 0.001$). EEG outcomes showed significant improvement, with the mean score for good EEG improving from 75.81 ± 14.21 to 17.97 ± 17.40 ($p < 0.001$). The mean score for poor EEG decreased from 87.93 ± 7.82 to 75.00 ± 14.83 ($p = 0.037$). Psychological assessments showed significant improvement, with the mean score increasing from 61.84 ± 13.95 to 67.76 ± 16.96 ($p < 0.001$).

Table 3: Comparison of the clinical seizure among the study subject before and after pulse therapy.

Seizure frequency per month	Before therapy	After therapy (5th cycle)	p-value
Frequent seizure	111.89 ± 311.36	0.02 ± 0.08	<0.001
Infrequent seizure	12.10 ± 39.71	0.71 ± 2.67	<0.001
Total	75.13 ± 251.39	0.27 ± 1.62	<0.001

Table 4: Clinical and Neuro electrophysiological outcome of study subject after IV MP pulse therapy (N=38).

Characteristics	Before therapy	After therapy (5th cycle)	p-value
Seizure			
Frequent	81.11 ± 12.90	28.71 ± 28.68	<0.001
Infrequent	71.93 ± 14.50	24.00 ± 24.50	<0.001
Electroencephalogram (EEG)			
Good	75.81 ± 14.21	17.97 ± 17.40	<0.001
Poor	87.93 ± 7.82	75.00 ± 14.83	0.037
Psychological assessment	61.84 ± 13.95	67.76 ± 16.96	<0.001

Discussion

This study focused on evaluating the effectiveness of intravenous methylprednisolone (IV MP) pulse therapy in treating Continuous Spike-Wave during Slow Wave Sleep (CSWS). The results were promising, showing that after 5 cycles of IV MP therapy, nearly all participants (97.4%) experienced complete seizure cessation (Figure 2). Additionally, significant improvements were observed in EEG outcomes in 55.2% of cases and neurocognitive improvements in 55.6% of cases. In a retrospective study involving 44 children with CSWS, Buzatu et al. reported a 77.2% positive response to steroids within the first three months of treatment, including EEG normalization in nearly

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half of the cases (47.73%) [16]. Another study by Kramer et al. [17] included 30 patients with ESES/CSWS, of whom 17 underwent various treatment regimens, including IV MP for 6–12 months [17]. Of these, 65% responded positively to the treatment, although some experienced relapse or developed steroid dependency. The age distribution of the study participants was primarily within the 6-10 age range, accounting for 63.16% of the total (Table 1). This is in line with the typical age of onset for CSWS, generally between 4 to 7 years, as noted in studies by Loddenkemper et al. [3] and Kessi et al. [5]. This age-specific prevalence underscores the critical need for early diagnosis and intervention. Delayed treatment can significantly impact neurodevelopmental outcomes, as highlighted by Sánchez Fernández et al [2]. The study also revealed a male predominance (63.16%) (Table 1), which aligns with previous studies indicating a higher incidence of CSWS in males [3,5]. This gender disparity raises questions about potential genetic or hormonal factors influencing the onset or progression of CSWS. Most participants in the study experienced focal seizures during sleep (89.47%) (Table 2), a hallmark feature of CSWS, consistent with descriptions in the literature [18,19]. The average lag period from seizure onset to the initiation of pulse therapy was about 3 years (Table 2), emphasizing the importance of earlier intervention for better neurocognitive outcomes [7,8]. One of the most notable findings of this study was the dramatic improvement in seizure control following IV MP pulse therapy. After completing the 5th cycle of treatment, an overwhelming 97.37% of participants showed significant improvements (Figure 1). This high response rate is clinically significant and aligns with recent literature, such as a multicenter study in 2021, which found corticosteroid treatments like MP to be more effective than traditional antiseizure medications (ASMs) in managing CSWS [20]. The study also reported significant reductions in both frequent and infrequent seizures (Table 3), suggesting that IV MP pulse therapy is effective across a range of seizure frequencies. This broad applicability as a treatment option is supported by multiple studies demonstrating seizure cessation, termination of Electrical Status Epilepticus during Sleep (ESES), and improvement in neuropsychological status following surgical interventions like hemispherotomy [21,22]. Furthermore, the study's findings on EEG outcomes substantiate the efficacy of IV MP pulse therapy (Table 4). EEG is a crucial diagnostic and monitoring tool in CSWS, and improvements in EEG patterns often indicate better seizure control and, consequently, better neurodevelopmental outcomes. Psychological assessments conducted before and after treatment also showed significant improvements, reinforcing the notion that effective seizure control is intrinsically linked to better cognitive outcomes. This aligns with the findings of Rho et al. [23] who posited that effective seizure management could lead to improvements in cognitive functions, thereby enhancing the quality of life for CSWS patients.

Limitations of the study

The study has several limitations. First, it was conducted at a single center, limiting its generalizability. Second, the short study duration hindered long-term cognitive assessment. Third, the lack of randomization could introduce bias. Lastly, the study did not include nocturnal polysomnographic EEG monitoring, missing potential insights into sleep-related aspects of CSWS.

Conclusion

The study provides compelling evidence for the efficacy of intravenous methylprednisolone pulse therapy in treating Continuous Spike-Wave during Slow Sleep (CSWS) in children. Significant improvements were observed in clinical seizure frequency, EEG outcomes, and psychological assessments. Despite the limitations, such as the single-center design and short duration, the findings offer a promising avenue for the management of this complex epileptic encephalopathy. Further multi-center, randomized trials with long-term follow-up are warranted to validate these results and explore the underlying mechanisms in greater depth.

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Conflict of interest: None declared

Ethical Approval: The study was approved by the Institutional Ethics Committee, BSMMU, Dhaka, Bangladesh

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