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Low Dose versus High Dose Steroids in Treatment of Viral Encephalitis

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ABSTRACT

Background: A number of illnesses, including viral infections, bacterial infections, parasitic infestation, toxin, and autoimmune reactions to vaccines, can result in encephalitis, a serious, potentially fatal condition.

Objective: The aim of the current study was to assess the effect of steroid pulse therapy versus low dose steroid on improvement of Glasgow Coma Scale (GCS), morbidity, and mortality among children with viral encephalitis.

Patients and methods: A randomised controlled, double-blind, clinical trial was carried out for from January 1, 2021 to December 31, 2021, at Assiut University Children Hospital (AUCH). All children treated for viral encephalitis at the Neurology Unit at AUCH during the research period were recruited. Participants were randomized into two groups: Group 1 (n=50) received dexamethasone on dose 0.6mg/kg per day for 5 days, while Group 2 (n=50) received steroid pulse therapy (high dose methylprednisolone on dose 30mg/ kg per day for 5 days) followed by short course of oral prednisolone over 6 weeks. **Results:** The 2 studied groups showed improvement over time (from baseline to day 1, and day 5), but the degree of improvement was much better in Group 2 (steroid pulse therapy group).

Conclusion: Steroid pulse therapy is effective, increases the possibility of full recovery and significantly reduces the duration of hospital stay needed for pediatric patients with viral encephalitis.

Keywords: Encephalitis, Steroids, Central nervous system infections, Adjunctive steroid therapy, Clinical trial, Assiut University.

INTRODUCTION

A person of any age at any time of the year who has encephalitis will have an acute onset of fever, a change in mental status, including indications like confusion, disorientation, coma, or immobility, and/or a new onset of seizures. Encephalitis is an inflammation of the brain parenchyma. A number of infections, including as viral infections, bacterial infections, parasite infestations, toxins, and autoimmune reactions to immunizations, can result in encephalitis, a serious, potentially fatal condition [(1)]. Neurological dysfunction brought on by encephalitis manifests itself in a wide variety of symptoms and indications. The afflicted areas of the central nervous system, the pathogenic agent, and other host factors all influence the clinical presentations, although there is considerable overlap in the clinical symptoms [(1)].

The majority of people who are affected by the uncommon viral infection known as acute viral encephalitis (VE) are children and young adults. It appears in persons of any age at any time of the year as an initial onset of fever, a change in mental status (including signs like confusion, disorientation, unconsciousness, or the inability to speak), and/or a new onset of seizures. There are several different neurotropic viruses that can cause acute VE [(2)].

Additionally, encephalitis of varying severity is connected to fresh infections every day, making accurate diagnosis challenging [(3)]. To establish the existence of encephalitis in the absence of pathologic evidence of brain inflammation, abnormal neuroimaging consistent with parenchymal affection or an inflammatory response in the CSF can be used as replacement markers of brain inflammation [(4)]. A medical emergency is acute VE. Serious neurological consequences and fatal outcomes are frequently seen. Early identification and therapy are the most important components in the management of acute VE [(1)].

The aim of the current study was to assess the effect of steroid pulse therapy versus low dose steroid on improvement of Glasgow Coma Scale (GCS), morbidity, and mortality among children with VE.

PATIENTS AND METHODS

A randomised controlled, double-blind, clinical trial was carried out for from January 1, 2021 to December 31, 2021 (total 12 months), at Assiut University Children Hospital (AUCH). All children treated for viral encephalitis at the Neurology Unit at AUCH during the research period were recruited.

Inclusion criteria: Boys and girls, ages ranging from one month to 18 years, and paediatric patients with a confirmed diagnosis of VE who guardians of the patients consent to participate in the study. The diagnosis of VE was confirmed by the clinical picture, investigations, and exclusion of other causes of encephalopathy.

Exclusion criteria: Any patient with aberrant renal function tests, any patient with abnormal liver function tests, and metabolic disorders are all examples of renal affliction (any patient with abnormal level of ammonia and lactate), patients with abnormal serum electrolytes, patients with previous seizure disorder or with any neurological disease and children or parents who refused to participate in this study.

Methodology

Eligible children were subjected to the following preliminary evaluation:

- **Personal data:** Name, age, sex, and residence.

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- Anthropometric measures: Height in cm and weight in kg.

- L**aboratory tests:** Complete blood count, renal function tests, liver function tests, serum electrolytes, cerebrospinal fluid (CSF) analysis, random blood glucose, C-reactive protein and blood and cerebrospinal fluid cultures**.**

- **Electroencephalogram (EEG)** and **neuroimaging (CT brain and MRI).**

Treatment protocol: Based on the computer generated sequence, the studied participants were randomized into two groups: **Group 1 (n=50)** received intravenous antibiotics (vancomycin and ceftriaxone), acyclovir on dose 20mg/kg every 8 hours and dexamethasone on dose 0.6mg/kg per day for 5 days. **Group 2 (n=50)** received intravenous antibiotics (vancomycin and ceftriaxone), acyclovir on dose 20mg/kg every 8 hours and steroid pulse therapy (high dose methylprednisolone on dose 30mg/ kg per day for 5 days) followed by short course of oral prednisolone over 6 weeks the (the first two weeks on dose 2mg/kg/day, the second two weeks on dose 1mg/kg/day then the last two weeks on dose 0.5 mg/kg/day).

Assessment for improvement will be according to Glasgow Coma Scale (GCS), motor power and other neurological examination.

Score of outcome: The outcome was listed as survived and passed away. The survivors were further classified as normal or those with mild, moderate, or severe disabilities, as follows: Normal: no ataxia, cranial nerve palsy, or motor deficit, and return to pre-illness functional level. Mild impairments include slight tone changes, deep tendon reflexes, isolated cranial nerve palsy, and grade 4 or ataxic weakness. Moderate impairment includes multiple cranial nerve involvement, moderate ataxia or weakness (grade 3), and behavioural disorder. Extreme impairments include quadriplegia, ataxia, and severe weakness (grade 3) [5].

Ethical Approval:

This study was ethically approved by the Institutional Review Board of the Faculty of Medicine, Assiut University. Written informed consent was obtained from guardians of all patients included in our study. This study was executed according to the code of ethics of the World Medical Association (Declaration of Helsinki) for studies on humans.

Statistical Analysis:

The collected data were introduced and statistically analyzed by utilizing SPSS (Statistical Package for Social Sciences; SPSS Inc., Chicago, IL, USA) version 22 for windows. Qualitative data were defined as numbers and percentages. Chi-Square test and Fisher's exact test were used for comparison between categorical variables as appropriate. Quantitative data were tested for normality by Kolmogorov-Smirnov test. Normal distribution of variables was described as mean and standard deviation (SD), or median and range when the data were not normally distributed. Because the data were not normally distributed, Mann Whitney U test and Kruskal-Wallis test were used to compare quantitative variables between two or more groups. The Freidman test was utilised to compare quantitative data that was not normally distributed across time (at baseline, day 1, and day 5). P value ≤ 0.05 was considered to be statistically significant.

RESULTS

Both studied groups were comparable with no significant difference between them as regarded age and sex **(Table 1).**

Table 1: Demographic data of the two studied groups (n=100).

Variable	Total (n=100)		Dexamethasone (n=50)		Methylprednisolone (n=50)		P-value
Age (years)							
Mean ± SD	3.85 ± 3.68		4.03 ± 3.82		3.67 ± 3.57		0.707
Median (range)	3 (2 months – 16 years)		3 (2 months – 15 years)		2.4 (3 months – 16 years)		
Sex, n (%)							
Male	55	(55%)	27	(54%)	28	(56%)	0.841
Female	45	(45%)	23	(46%)	22	(44%)	

Quantitative data are presented as mean ± SD and median (range), qualitative data are presented as number (percentage), Significance defined by $P \leq 0.05$.

The presenting symptoms of the studied cases were summarized in **Table 2**. Comparing the presenting symptoms of the studied cases between both studied groups, we found no statistical significant difference between them (P>0.05, for all).

Table 2: Presenting symptoms of the two studied groups (n=100).

Variable	Total (n=100)		Dexamethasone (n=50)		Methylprednisolone (n=50)		P-value
History of fever							
• Absent	27	(27%)	11	(22%)	16	(325)	0.260
• Present	73	(73%)	39	(78%)	34	(68%)	
Convulsions							
• Absent	31	(31%)	18	(36%)	13	(26%)	0.280
• Present	69	(69%)	32	(64%)	37	(74%)	
Irritability							
• Absent	76	(76%)	40	(80%)	36	(72%)	0.349
• Present	24	(24%)	10	(20%)	14	(28%)	
Vomiting							
• Absent	77	(77%)	39	(78%)	38	(76%)	0.812
• Present	23	(23%)	11	(22%)	12	(24%)	
Associated symptoms							
• No	53	(53%)	23	(46%)	30	(60%)	0.161
• Yes	47	(47%)	27	(54%)	20	(40%)	
▪ Diarrhea	16	(16%)	10	(20%)	6	(12%)	
▪ Rhinorrhea	15	(15%)	7	(14%)	8	(16%)	
▪ Cough	14	(14%)	8	(16%)	6	(12%)	
▪ Rash	2	(2%)	2	(4%)	0	(0.0%)	
Hallucinations							
• Absent	86	(86%)	44	(88%)	42	(84%)	0.564
• Present	14	(14%)	6	(12%)	8	(16%)	

Qualitative data are presented as number (percentage), Significance defined by P ≤0.05.

Table 3 shows that by comparing the results of vital signs examinations of the studied cases between both studied groups, we found no statistical significant difference between them (P>0.05, for all).

Table 3: Result of the vital signs examinations of the two studied groups (n=100).

Variable	Total (n=100)		Dexamethasone (n=50)		Methylprednisolone (n=50)		P-value
Blood pressure							
• Normal	100	(100%)	50	(100%)	50	(100%)	-----
• Hypertensive	0	(0.0%)	0	(0.0%)	0	(0.0%)	
• Hypotensive	0	(0.0%)	0	(0.0%)	0	(0.0%)	
Heart rate							
• Normal	58	(58%)	28	(56%)	30	(60%)	0.685
• Tachycardia	42	(42%)	22	(44%)	20	(40%)	
Respiratory rate							
• Normal	51	(51%)	25	(50%)	26	(52%)	0.978
• Tachypnea	39	(39%)	20	(40%)	19	(38%)	
• Bradypnea	10	(10%)	5	(10%)	5	(10%)	
Temperature							
• Normal	10	(10%)	7	(14%)	3	(6%)	0.182
• Increased	90	(90%)	43	(86%)	47	(94%)	
GCS at baseline							
• Mean ± SD	8.13 ± 3.52		8.30 ± 3.88		7.96 ± 3.15		0.424
• Median (range)	8 (3 – 13)		9 (3 – 13)		8 (3 – 13)		

Quantitative data are presented as mean ± SD and median (range), qualitative data are presented as number (percentage), Significance defined by P ≤0.05.

Table 4 shows that by comparing the results of laboratory data of the studied cases between both studied groups, we found no statistical significant difference between them (P>0.05, for all).

Table 4: Result of the laboratory data of the two studied groups (n=100).

Variable	Total (n=100)		Dexamethasone (n=50)		Methylprednisolone (n=50)		P-value
WBCs count							
• Normal	31	(31%)	13	(26%)	18	(36%)	0.280
• Leukocytosis	69	(69%)	37	(74%)	32	(64%)	
WBCs differential							
• Lymphocyte predominance	44	(63.8%)	21	(56.8%)	23	(71.9%)	0.193
• Neutrophil predominance	25	(36.2%)	16	(43.2%)	9	(28.1%)	
CSF cell differential							
• Lymphocyte predominance	42	(64.6%)	21	(63.6%)	21	(65.6%)	0.867
• Neutrophil predominance	23	(35.4%)	12	(36.4%)	11	(34.4%)	
CSF cell count							
• Mean ± SD	24.74 ± 5.96		24.10 ± 4..08		25.38 ± 4.51		0.756
•							
Random blood glucose							
• Mean ± SD	117.16 ± 13.79		118.22 ± 12.80		116.10 ± 14.78		0.173
•							
C reactive protein							
• Mean ± SD	22.91 ± 5.80		23.16 ± 6.26		22.66 ± 4.48		0.901
•							
CSF glucose							
• Mean ± SD	70.56 ± 9.02		71.52 ± 7.91		69.60 ± 9.99		0.069
CSF/serum glucose ratio							
• Mean ± SD	0.60 ± 0.02		0.60 ± 0.02		0.59 ± 0.02		0.200
CSF protein							
• Mean ± SD	20.89 ± 4.79		20.62 ± 3.05		21.16 ± 3.59		0.388

Quantitative data are presented as mean ± SD and median (range), qualitative data are presented as number (percentage), Significance defined by P ≤0.05.

No significant difference was observed between both studied groups as regard to MRI or EEG finding (**Table 5)**.

Table 5: Electroencephalogram and Neuroimaging finding of the studied patients (n=100).

Variable	Total (n=100)		Dexamethasone (n=50)		Methylprednisolone (n=50)		P-value
CT							
• Normal	52	(52%)	32	(64%)	20	(40%)	**0.016***
• Detection of lesion on CT	48	(48%)	18	(36%)	30	(60%)	
MRI							
• Normal	19	(19%)	10	(20%)	9	(18%)	0.265
• Detection of lesion on MRI	56	(56%)	31	(62%)	25	(50%)	
• Not done	25	(25%)	9	(18%)	16	(32%)	
EEG							
• Normal	48	(48%)	23	(46%)	25	(50%)	0.775
• Abnormal	29	(29%)	14	(28%)	15	(30%)	
▪ Focal	19	(19%)	9	(18%)	10	(20%)	
▪ Others	10	(10%)	5	(10%)	5	(10%)	
• Not done	23	(23%)	13	(26%)	10	(20%)	

Qualitative data are presented as number (percentage), Significance defined by P ≤0.05.

It was found that both treatment groups show improvement over time (from baseline to day 1, and day 5), but the degree of improvement was much better in pulse therapy group **(Figure 1)**.

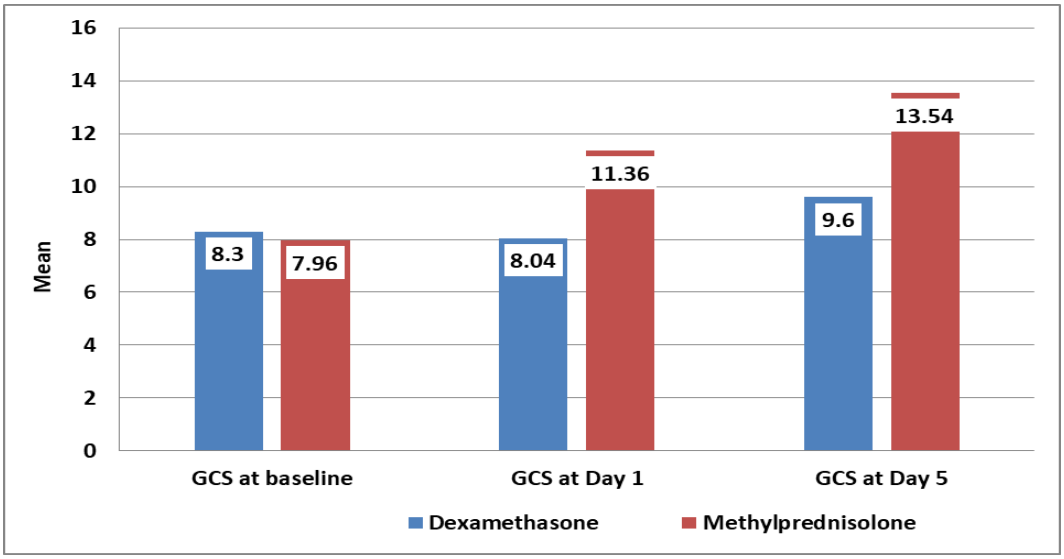

Figure 1: Bar graph showing difference in GCS from the baseline, day 1, and day 5 between both studied groups.

By comparing the outcome of the studied participants according to the received treatment protocol we observed that, no significant difference was found between both studied groups as regard to death status (P=0.065); however, among patient who were survived the rate of full recovery was significantly higher in patients who received pulse therapy with Methylprednisolone (P=0.017) as shown in **Table 7.**

Table 7: Outcome of the studied participants according to the received treatment protocol (n=100).

Outcome	Dexamethasone (n=50)		Methylprednisolone (n=50)		P-value
• Died	9	(18%)	3	(6%)	0.065
• Survived	41	(82%)	47	(94%)	
▪ Full recovery	9	(22%)	21	(44.7%)	**0.017***
▪ Mild	12	(29%)	15	(31.9%)	
▪ Moderate	10	(24.4%)	9	(19.1%)	
▪ Severe	10	(24.4%)	2	(4.3%)	

Qualitative data are presented as number (percentage), Significance defined by P ≤0.05.

Duration of hospital stay was significantly shorter in patients who received pulse therapy with Methylprednisolone as compared to patients who received Dexamethasone (21.88 ± 9.57 versus 14.04 ± 5.17, P=0.017) in both studied groups respectively **(Figure 2).**

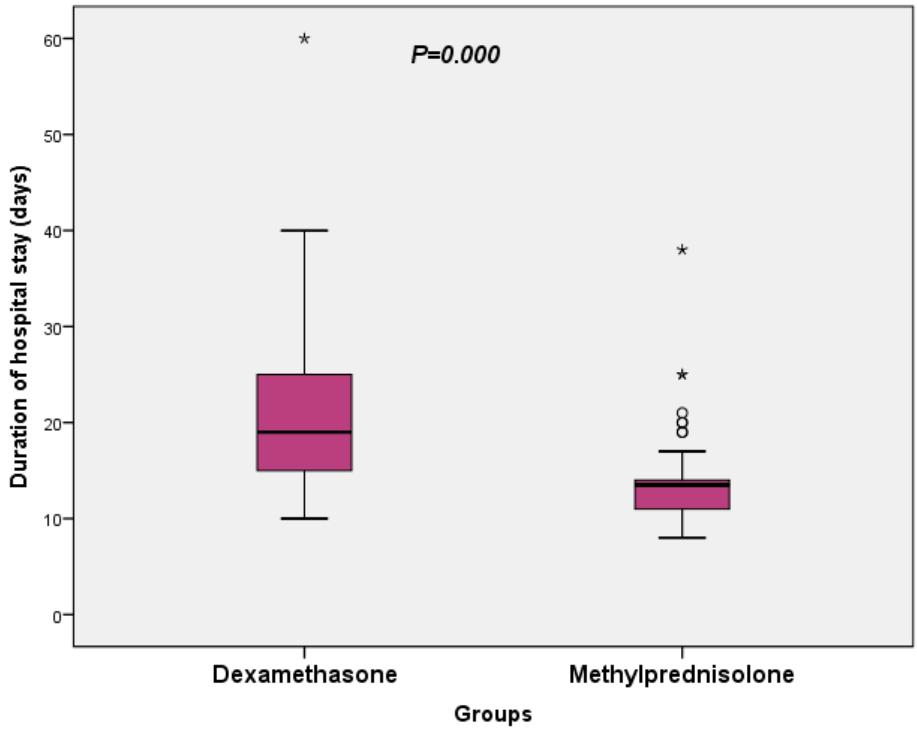

Figure 2: Box Plot graph showing difference in hospital stay (days) between both studied groups.

DISCUSSION

In rodent and pre-clinical models, the use of adjuvant corticosteroid therapy with acyclovir has demonstrated to be effective, with a decrease in the severity of infection, positive long-term benefits, and no increase in viral burden [(6)]. Despite this evidence, the use of corticosteroid therapy is only evaluated by a small amount of clinical data. The present study is a one-year double blind randomized controlled clinical trial aimed to assess the effect of steroid pulse therapy versus low dose steroid in treatment of VE regarding the effect on GCS, morbidity and mortality, also to improve the outcome in pediatric patients who admitted to AUCH in the period from January 1, 2021 to December 31, 2021. The study included 100 pediatric patients with confirmed VE.

Both studied groups were comparable with no significant difference between them as regarded to age and sex (P-values 0.707 and 0.841, respectively). The median age of the studied participants was 3 years and ranged from 2 months up to 16 years old. Out of 100 studied participants 55% were males and 45% were females.

In line with our study is the recent Egyptian study of **Meligy *et al.*** [(7)]. That study described the aetiology, demographic characteristics, clinical picture, short-term outcome, and risk factors of mortality of children with VE in Egyptian children. The mean age of the patients under study was 29.34 (SD 28.29) months and ranged from 1 month to 12 years. Of the 96 participants in the study, 60 (62.55%) were men and 36 (37.5%) were women. The median age of the children with herpes simplex encephalitis who were the subject of **De Blauw *et al.*** [(8)] investigation, which sought to gain more knowledge about the clinical presentation, aetiology, and clinical prognosis of children in the Netherlands with severe encephalitis, was 1.73 years (IQR 0.77 - 5.01). All studied participants have normal blood pressure, 42% suffered from tachycardia, 39% suffered from tachypnea, 10% suffered from bradypnea, 90% were feverish (defined as a temperature >38.5°C).

The median GCS at baseline for whole studied cases was 8 and ranged from 3-13. By comparing the results of vital signs examinations of the studied cases between both studied groups, we found no statistical significant difference between them (P>0.05, for all). Leukocytosis was documented in 69% of the studied cases, for WBCs differential; 44 (63.8%) have lymphocyte predominance, and 25 (36.2%) have neutrophil predominance.

The following variables were used to define the features of cerebrospinal fluid: white blood cell count (/L), protein levels (mg/L), and glucose levels; we compared glucose levels between CSF and blood. We assessed protein levels and white blood cell count based on the previously established age-specific cutoff values **[(9)].** We found that for CSF cell differential; 42 (64.6%) have lymphocyte predominance, and 23 (35.4%) have neutrophil predominance, the median CSF cell count was 20 (ranged from 0 up to 150), the median random blood glucose was 116 (ranged from 82 up to 158), the median C reactive protein was 21 (ranged from 6 up to 121), the median CSF glucose was 70 (ranged from 40 up to 98), the median CSF/serum glucose ratio was 0.6 (ranged from 0.55 up to 0.66), and the median CSF protein was 19 (ranged from 14 up to 45).

By comparing the results of laboratory data of the studied cases between both studied groups, we found no

statistical significant difference between them (P>0.05, for all). A total of 100 CT scans were performed in all, and 48.0% of them revealed anomalies (diffuse and focal cerebral swelling or oedema). A total of 75 MRIs were done, and 56% of them revealed abnormalities (focal and diffuse lesions). A total of 77 instances had an EEG conducted, and 29% of those had abnormalities. In the majority of instances where an EEG was done (65.5%), focal lesions were found. Regarding the MRI or EEG findings, there was no discernible difference between the 2 study groups (P-values 0.265 and 0.775, respectively).

The death rate was not different between the 2 research groups in the current investigation, as well (P=0.065). However, patients who had pulse therapy with methylprednisolone had a considerably greater rate of full recovery (P=0.017). Patients who received pulse treatment with methylprednisolone had significantly shorter hospital stays (P=0.017). Regarding the outcome severity and mortality status according to the participants' age and sex, there was no discernible difference between the 2 study groups (P values 0.085 and 0.108, respectively). Based on these results, we recommended pulse therapy combined with methylprednisolone as an adjuvant therapy for paediatric VE patients. Before the discovery of acyclovir, steroids were widely employed as the primary therapy for herpes-simplex VE [(10)].

Our expertise does not fully explain the role that steroids play in the treatment of HSVE patients. Animal models are where the majority of data on steroid effects in HSVE comes from (that is, mouse, rat and rabbit). There have been reports on the results of HSVE animal model treatment with acyclovir and corticosteroids [(6)]. According to the data, Animals administered acyclovir plus corticosteroids had HSV virus loads in their brain tissue that were comparable to those of animals given acyclovir alone. These studies also demonstrated that corticosteroids do not affect acyclovir's antiviral action while having the potential to lower the severity of HSVE infection. Furthermore, it has been suggested that a host immune response to HSVE, such as one involving cytokines, may have an impact on the outcome of HSVE [(11)]. As a result, reducing cerebral oedema and controlling the host immune response associated with the acute stage of HSVE may be part of the pharmacological mechanism of corticosteroid treatment in the acute stage of the disease [(12)].

Also controversial is the use of high dosages of corticosteroids (methylprednisolone or dexamethasone) in cases of acute infectious encephalitis. While steroids may be particularly advised in some circumstances, such as tuberculous meningoencephalitis or granulomatous angiitis following varicella zoster infection, their effectiveness in the presence of acute VE is unknown and they cannot be routinely advised.Our finding was supported by the previous studies in chronological order; **Upton *et al.* [(13)]** and **Habel & Brown [(14)]** reported improved outcome in trial of using Dexamethasone as an isolated treatment of herpes-simplex encephalitis. Also, the last author reported EEG improvement among patients with Dexamethasone.

Kamei *et al.* [(12)] have conducted a non-randomized retrospective study with 45 HSVE patients. With older age, a lower GCS score after starting acyclovir, and no corticosteroid therapy, a negative prognosis was obvious. Age, GCS upon admission, and lack of corticosteroid therapy were all highly significant independent predictors of prognosis. In our study we find no difference in disease severity according to age of the studied participants, this difference could be attributed to difference in the age range that is included in the study of **Kamei *et al.* [(12)]** as the author include adult patients with HSE, meanwhile our study include only pediatric patients. The patient's mental and physical condition improved after receiving dexamethasone (4*10 mg, 4 days) as an adjuvant to acyclovir, although a neuropsychological test revealed that the patient had poor spatial orientation. This case study by **Mesker *et al.*** [(15)] involved a 30-year-old pregnant woman. Despite the fact that adjunctive corticosteroids are frequently given to patients with cerebral oedema and high intracranial pressure to reduce inflammation [(16)], more research, such as clinical prospective randomised controlled studies, are required to determine the ideal corticosteroid type, dosage, and duration for treating VE.

CONCLUSION

Steroid pulse therapy is effective, increases the possibility of full recovery and significantly reduces the duration of hospital stay needed for pediatric patients with VE.

Declarations:

Consent for publication: I attest that all authors have agreed to submit the work.

Availability of data and material: Available

Competing interests: None

Funding: No fund

Conflicts of interest: no conflicts of interest.

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