DOI: https://doi.org/10.53555/nnmhs.v9i8.1818 Publication URL: https://nnpub.org/index.php/MHS/article/view/1818

ANTIVIRAL THERAPY FOR HERPES SIMPLEX VIRUS ENCEPHALITIS: SYSTEMATIC REVIEW

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Abstract

Introduction: *Without regard to treatment, herpes simplex encephalitis is detrimental. Neonatal encephalitis caused by HSV-2 affects the brain more extensively, resulting in more neurologic complications. Viral variables and host immune responses determine virulence and invasiveness in adults. In order to maintain latency, it is necessary to inhibit viral lytic-phase genes and modify innate and adaptive immune responses to thwart host cellular defenses.*

The aim: *This article explore effectiveness and safety antiviral therapy for herpes simplex virus encephalitis.*

Methods: *By comparing itself to the standards set by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study was able to show that it met all of the requirements. So, the experts were able to make sure that the study was as up-to-date as it was possible to be. For this search approach, publications that came out between 2013 and 2023 were taken into account. Several different online reference sources, like Pubmed and SagePub, were used to do this. It was decided not to take into account review pieces, works that had already been published, or works that were only half done.*

Result: *In the PubMed database, the results of our search brought up 67 articles, whereas the results of our search on SagePub brought up 53 articles. The results of the search conducted for the last year of 2010 yielded a total 11 articles for PubMed and 3 articles for SagePub. In the end, we compiled a total of 8 papers, 7 of which came from PubMed and one of which came from SagePub. We included two research that met the criteria.*

Conclusion: *The standard treatment of HSV-1 encephalitis is IV acyclovir, as PO acyclovir and valacyclovir require multiple doses per day.*

Keyword: *Acyclovir; Antiviral therapy; Encephalitis; Herpes simplex virus; Valacyclovir*

INTRODUCTION

Herpetic infections were documented in ancient Greek literature. Large double-stranded DNA viruses are herpes. Eight herpes viruses afflict humans. Acute or subacute herpes simplex encephalitis caused by type 1 (HSV-1) or type 2 (HSV-2) viruses causes focal or widespread brain dysfunction. Most herpes simplex encephalitis is caused by HSV-1, with HSV-2 accounting for less than 10%.[1,2] HSV-1, the most common cause of lethal encephalitis, occurs sporadically and non-seasonally worldwide and causes almost all herpes encephalitis after the neonatal period. Despite antiviral treatment, adult HSV-1 causes severe morbidity and death.[3,4]

Herpes simplex encephalitis is harmful, regardless of treatment. HSV-2-induced neonatal encephalitis affects the brain more broadly, causing more neurologic complications. In adults, viral variables and host immune responses dictate virulence and invasiveness. The complicated methods that preserve latency include suppressing viral lytic-phase genes and altering innate and adaptive immune responses to abort host cellular defense mechanisms. HSV-1 often causes oral lesions (fever blisters) that may recur with decreasing frequency, severity, and length. Genital lesions usually arise one to two weeks following HSV-2 infection.[5]

The brain is impacted by peripheral spread or viremia. Three mechanisms are thought to allow HSV-1 to enter the brain from the peripheral site of infection. The initial path is trigeminal or olfactory nerves from the primary oro-pharyngeal infection to the brain.[4] The second method uses the same neural circuits as periphery infection reactivation. The last mechanism is solely related to brain HSV-1 reactivation. Globally, HSV-1 is the leading cause of life-threatening sporadic encephalitis and does not exhibit seasonal variation. Globally, 60 to 90 percent of older individuals are seropositive for HSV-1.[3,6,7]

A survey conducted in the United States between 2005 and 2010 among people aged 14 to 49 found that approximately 54% and 16%, respectively, were positive for HSV-1 and HSV-2. The annual incidence of herpes simplex encephalitis is between two and four per one million people worldwide. Ten to twenty percent of the 20,000 annual viral encephalitis patients in the United States are affected by HSV-1 encephalitis.[3] A population-based multicenter study identified herpes simplex as the leading cause of infectious encephalitis in the United Kingdom. HSV is once again the most frequently identified pathogen in hospitalized encephalitis patients in Australia.[7]

The incidence of HSV-1 encephalitis appears to be nearly identical in Sweden and the United States, as demonstrated by studies conducted in both nations. Although all age categories are affected, children and the elderly are most frequently and severely affected. Nearly one-third of the cases occurred in infants and adolescents, while fifty percent of the patients were older than fifty years.[7] Herpes simplex encephalitis (HSE) is not indicated by any of the clinical symptoms. Therefore, the diagnostic evaluation must be expedited without impeding treatment. There must be a high index of suspicion, notably in immunocompromised patients presenting with febrile encephalopathy.[5,8]

The emergency management strategy includes an evaluation of the airway, respiration, and circulation, as well as the implementation of appropriate measures. In suspected cases, a lumbar puncture must be performed if brain imaging does not reveal evidence of intracranial hypertension or a space-occupying lesion. All adults with suspected or confirmed HSE must receive intravenous (IV) acyclovir at a dose of 10 mg per kilogram of body weight every 8 hours. In uncommon cases where IV acyclovir is unavailable, IV ganciclovir may be substituted. Typically, foscarnet or cidofovir are administered intravenously to manage acyclovir resistance.[8–11]

This article investigates the efficacy and safety of antiviral therapy for herpes simplex virus encephalitis.

METHODS

The author of this study verified that it adhered to the standards by adhering to Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines. This is done to ensure that the investigation's findings are accurate. This literature review was conducted to investigate the efficacy and safety of antiviral therapy for herpes simplex virus encephalitis. As the primary purpose of this paper, the relevance of the identified challenges will be emphasized throughout.

To participate in the investigation, researchers had to meet the following requirements: 1) The paper must be written in English and investigate the efficacy and safety of antiviral treatment for herpes simplex virus encephalitis. For the manuscript to be considered for publication, it must satisfy both of these requirements. 2) A number of the articles examined were published after 2010, but prior to the time period deemed pertinent by this systematic review. Editorials, submissions without a DOI, previously published review articles, and entries essentially identical to previously published journal articles are not permitted.

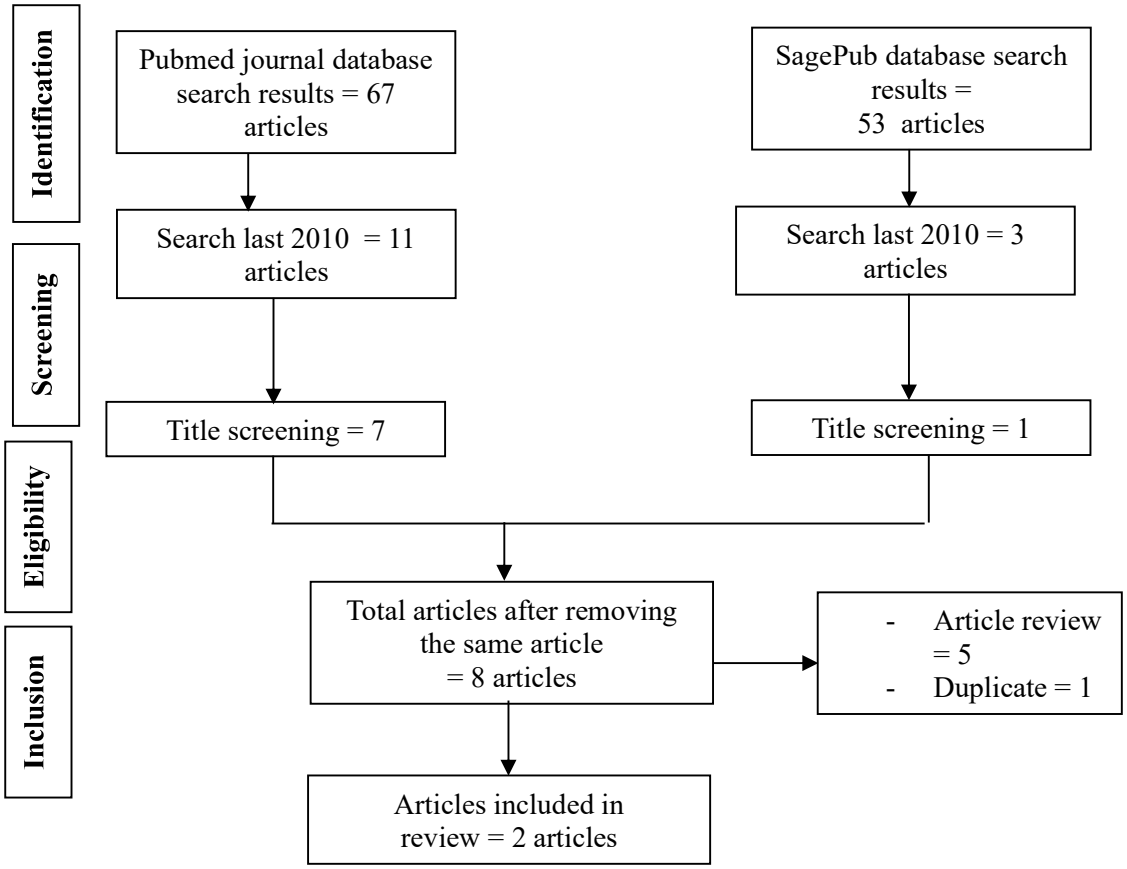

Figure 1. Article search flowchart

We used "effectiveness"; "safety"; "antiviral therapy"; "herpes simplex virus"; and "encephalitis" as keywords.The search for studies to be included in the systematic review was carried out from August, 17th 2023 using the PubMed and SagePub databases by inputting the words: *(("antivir ther"[Journal] OR ("antiviral"[All Fields] AND "therapy"[All Fields]) OR "antiviral therapy"[All Fields]) AND ("simplexvirus"[MeSH Terms] OR "simplexvirus"[All Fields] OR ("herpes"[All Fields] AND "simplex"[All Fields] AND "virus"[All Fields]) OR "herpes simplex virus"[All Fields]) AND ("encephalities"[All Fields] OR "encephalitis"[MeSH Terms] OR "encephalitis"[All Fields])) AND ((y_10[Filter]) AND (clinicaltrial[Filter] OR randomizedcontrolledtrial[Filter]))* used in searching the literature.

The authors examined the abstract and title of each study to determine whether or not it met the inclusion criteria. The authors then determined which previous studies would serve as sources for the article and chose those studies. This conclusion was reached after analyzing numerous studies that all appeared to indicate the same trend. All submissions must be written in English and must be previously unpublished. For the systematic review, only publications meeting all inclusion criteria were considered.

This narrows the search results to only those that are pertinent to your search. We disregard the findings of any study that does not meet our criteria. The research findings will then be analyzed in depth. The research conducted for this study revealed the following information: names, authors, publication dates, location, study activities, and parameters. Each author conducted independent research on the research included in the publication's title and abstract prior to deciding which publications to investigate further.

The next stage is to evaluate all of the articles that meet the review's inclusion criteria. Then, based on the findings, we will choose which articles to include in the review. This criterion is used to select documents for further analysis. To facilitate the selection of papers for evaluation as much as feasible. This section discusses the prior studies conducted and the aspects of those studies that made their inclusion in the review appropriate.

RESULT

In the PubMed database, the results of our search brought up 67 articles, whereas the results of our search on SagePub brought up 53 articles. The results of the search conducted for the last year of 2010 yielded a total 11 articles for PubMed and 3 articles for SagePub. In the end, we compiled a total of 8 papers, 7 of which came from PubMed and one of which came from SagePub. We included two research that met the criteria.

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Agent	Result
Gnann, 2015[10]	Swedeen	Randomized clinical trial	87 adult patients with HSE	Valacyclovir (VACV) 2 g thrice daily (n = 40) or placebo tablets (n = 47) (12 tablets of study medication daily)	Following the conventional treatment of intravenous ACV for PCR-confirmed HSE, an extra 3-month course of oral VACV therapy did not provide a further advantage when determined by neuropsychological testing 12 months later in a population of survivors with relatively high levels of functioning.
Pouplin , 2011[12]	Vietnam	Randomized clinical trial	Nine patients (5 males, 4 females)	Valacyclovir at 1,000 mg three times daily, full 21-day course	Throughout the entirety of the treatment for herpes encephalitis, individuals who took valacyclovir orally at a dosage of 1,000 milligrams (mg) three times per day for 21 days reached therapeutic levels in their cerebrospinal fluid (CSF). It is possible that a weakened and more permeable BBB was the cause of the greater levels of acyclovir found in the CSF during the initial stages of treatment.

Gnann, et al (2015)[10] showed there were no statistically significant differences in age, sex, or race between the two randomization groups, and their demographic characteristics were statistically comparable. At 12 months, there was no significant difference in the MDRS scoring for VACV-treated vs. placebo receivers, with 85.7% and 90.2%, respectively, of patients displaying no or slight cognitive impairment (P = 0.72). This was determined by comparing the percentage of patients who had no or mild impairment after receiving either treatment. In none of the treatment groups, there were any notable adverse events that may be linked to the research.

Pouplin, et al (2011)[12] showed the 2-h-postdose concentrations of acyclovir in plasma remained stable from day 2 to the end of the treatment, with the mean steady-state concentration around 28.1 ± 9.8 μM, whereas the 2-h-postdose concentrations in CSF reached maximum levels on day 2 (6.5 ± 4.5 μM) and then on days 10 (4.2 ± 3.8 μM) and 20 (3.5 ± 1.7 μM μM) decreased to concentrations similar to and lower than that of the first day of treatment (3.6 ± 1.7 μM). The CSF/plasma concentration ratio was calculated to determine the blood/CSF levels of acyclovir over the treatment period. The concentrations of acyclovir in plasma remained stable from the beginning of steady state (day 2) to the end of the treatment, whereas the concentrations in CSF decreased after day 2. The 2-h-postdose CSF / plasma acyclovir concentration ratio was 22.9% on day 2, 14.5% on day 10, and 12.0% on day 20. The acyclovir CSF/plasma ratio dropped to approximately 50% within 18 days of steady state.

DISCUSSION

The herpes simplex virus (HSV) is the causative agent in the vast majority of cases of sporadic acute viral encephalitis across the globe; HSV-1 is accountable for approximately 90% of these cases, whereas immunocompromised patients are typically infected by HSV-2.[13] At this time, it is believed that the incidence of HSE in the United States is between two and four per 1,000,000, and up to 55% of healthy persons between the ages of 30 and 50 have a seropositive result for HSV-1. The most typical symptoms of HSE are feeling sick, throwing up, having headaches, having focus deficits, becoming confused, and having seizures.[14]

The temporal lobe, the trigeminal nerve, and the brainstem are the typical areas that are infected by HSV. This infection might potentially cause amnesia, neurogenic pain, and upward gaze palsies. Usually, symptoms appear suddenly and can lead to a loss of consciousness, which results in approximately one third of patients requiring admission to an intensive care unit and intubation. Patients with a weakened immune system are at an increased risk of developing venous thromboembolism, incorrect antidiuretic hormone secretion, and secondary infections. Increased intracranial pressure is the most dangerous complication of HSE, and it can lead to uncal and / or transtentorial herniation.[15,16]

Recent research conducted by Kiyani and colleagues looked into the mortality rate of patients diagnosed with viral encephalitis, as well as the costs associated with providing treatment to these patients. Over 8,000 people in the MarketScan database were diagnosed with viral encephalitis between 2008 and 2015, and of them, 38.3% were confirmed to have HSV-1 encephalitis. This was determined through a retrospective study of the database.[17] The residual morbidity survivors got a variety of treatments. Three patients took acyclovir and foscarnet without corticosteroids, while one received both. Foscarnet was given five to seven days after acyclovir for acyclovir-resistant HSV. Acyclovir-resistant HSV consistently occurs in 0.3% of immunocompetent patients.[18]

The emergency management plan includes a check of the lungs, breathing, and blood flow, as well as the use of the right steps. If brain imaging doesn't show any signs of intracranial hypertension or a space-occupying tumor, a lumbar puncture must be done in suspected cases. All people with suspected or confirmed HSE must get 10 mg per kilogram of body weight of acyclovir through an IV every 8 hours. If IV acyclovir isn't available, sometimes IV ganciclovir can be used instead. Most of the time, foscarnet or cidofovir are given through an IV to treat acyclovir resistance.[8–11,16]

Individuals who took valacyclovir orally at a dosage of 1,000 milligrams (mg) three times per day for 21 days obtained therapeutic levels in their cerebrospinal fluid (CSF) during the length of the therapy for herpes encephalitis. This was accomplished by lowering the viral load in the CSF. It is probable that a weakened and more permeable BBB was the reason of the increased amounts of acyclovir that were identified in the CSF during the initial phases of treatment. This hypothesis is supported by the findings of a study published in Neurology.[12]

The viral DNA polymerase (UL30) is responsible for the elongation of the viral genome during replication. Numerous antivirals that have been licensed for the treatment of HSV-1 and HSV-2 infections are acyclic nucleoside and nucleotide analogs.[19] These analogs interfere with the elongation of the viral genome. Acyclovir (ACV) is an acyclic guanosine analog that was identified in the sponge Cryptotethya crypta. It is the substance that is currently used the most commonly to treat herpes simplex virus types 1 and 2, primarily due to the fact that it is inexpensive, well tolerated, and safe.[20]

Importantly, in order for acyclovir to exercise its antiviral effect, it must first be activated within the cell by being phosphorylated into acyclovir triphosphate. This can only be done intracellularly. This process is carried out by the viral thymidine kinase (TK, UL23 gene), which catalyzes acyclovir into acyclovir monophosphate. This results in an increase in the concentration of acyclovir within infected cells by decreasing the amount that is allowed to leave the cell. Once in its triphosphate state, acyclovir becomes a substrate for the viral DNA polymerase, hence interfering with the process of DNA synthesis.[20]

Additional phosphorylations are carried out by cellular kinases. Importantly, inhibiting the synthesis of new viral genome copies, which results in the generation of fewer novel infectious viral particles, does not have an effect on viruses that are dormant within the neurons of the host and, as a result, does not cure infection. In addition to ACV, there are additional options for treating skin lesions caused by herpes simplex viruses, including valacyclovir, penciclovir, and famciclovir, which are also considered first-line medications for treating HSV-1 and HSV-2 and are therefore frequently used. [20]
These compounds are nucleic acid analogs with a shared mechanism of action that inhibits the function of viral DNA polymerase, similar to ACV. Valacyclovir is also approved for the treatment of HSV-1 and HSV-2 infections and clinical manifestations generated by HSV-1 and HSV-2, such as cold sores and recurrent genital herpes, in addition to VZV and cytomegalovirus. In addition, famciclovir is authorized for the treatment of herpes viruses, including HSV-1 and HSV-2 (genital herpes and orolabial herpes), as well as VZV.[21]

CONCLUSION

IV acyclovir is the standard treatment for HSV-1 encephalitis because PO and valacyclovir require numerous daily doses. IV acyclovir with adjuvant corticosteroids for HSV-1 encephalitis has no defined treatment guidelines. Acyclovir is recommended for all suspected viral encephalitis patients. Since no specific treatment protocol exists, doctors must utilize their professional judgment while treating this patient population.

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