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Research Article

Effect of Oral Acyclovir on Hospitalized Children with Infectious Mononucleosis: A Double-blind Clinical Trial

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ABSTRACT

Background and objectives: Infectious mononucleosis is a disease mainly caused by Epstein-Barr virus. The disease is most frequently observed in children. Acyclovir is a nucleoside analogue with high in-vitro antiviral activity. The present study was performed to evaluate the therapeutic effect of oral acyclovir on hospitalized children with infectious mononucleosis.

Methods: This randomized double-blind clinical trial was performed on 48 patients with infectious mononucleosis who were randomly divided into an intervention (n=22) and a control (n=26) group. The intervention group received 80 mg/kg/day oral acyclovir q.i.d. for five days and the control group received placebo (Starch capsule, Barij Essence). Clinical symptoms, test results, drug side effects and demographic information of the patients were recorded in a checklist. Data were analyzed using SPSS 18. Descriptive statistics including mean and standard deviation were used to describe data. The chi-square and Mann-Whitney tests were used for comparison of data. All analysis was carried out at significance of 0.05.

Results: The mean age of patients in the treatment and control groups was 5.67± 2.82 and 6.94± 3.43 years, respectively (p=0.50). The symptoms of infectious mononucleosis e.g. fever, exudative erythema, tonsillitis, lymphadenopathy, tenderness, hepatomegaly and splenomegaly did not differ significantly between the two groups (p>0.05). In addition, the mean duration of hospitalization in the intervention and control groups was 4.23 ± 1.71 and 5.85 ± 7.27 days, respectively (p=0.65).

Conclusion: The use of acyclovir-based regimens in the treatment of patients with infectious mononucleosis still depends on clinical suspicion and the experience of the treating physician, and its routine use is not recommended.

Keywords: Infectious mononucleosis; Acyclovir; Clinical symptoms; Decreased course of treatment

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Introduction

Infectious mononucleosis is a disease that mostly affects children, adolescents and young adults. Symptoms include fever, fatigue, exudative pharyngitis and cervical lymphadenopathy. In addition, atypical lymphocytosis is a common laboratory finding in patients with infectious mononucleosis. About 90% of infectious mononucleosis cases are caused by the Epstein-Barr virus (EBV), which has the ability to be remain latent in the body for a long time and later reactivate in special circumstances (1). The most common cause of late infectious mononucleosis is the cytomegalovirus (2). Infectious mononucleosis is more common in developing countries, particularly among children aged 3-4 years. However, in developed countries, the disease may also develop until adolescence (1). In developed countries, most studies on infectious mononucleosis have been focused on the elderly whilst the peak incidence of infection is in the age range of 15 to 24 years. In the UK, studies showed that infectious mononucleosis in the elderly is associated with an increased need for hospitalization (3). Diagnosis is mostly based on clinical and laboratory findings, and detecting atypical lymphocytes in the peripheral blood smear as well as mono-test or heterophilic antibody test (Paul-Bunnell test) help the diagnosis. However, the most definitive diagnostic test for primary and acute infectious mononucleosis is IgM antibody against IgM-EBV-VCA-Ab capsid virus (4).

Generally, the total incubation period of EBV is four to seven weeks. Moreover, mononucleosis is a self-limiting disease and spontaneous recovery occurs in two to three weeks. However, symptoms may persist for several weeks, causing serious discomfort in the patients. In some cases, the infection can lead to chronic or recurrent disease or even death (5). Complications include stridor, respiratory distress, hemolytic anemia, bone marrow suppression, low blood counts (especially thrombocytopenia), bleeding, meningoencephalitis or other neurological complications, involvement of other organs of the body, and eventually malignancies such as nasopharyngeal carcinoma in adults and Burkitt lymphoma in children (6).

Steroids are used for their anti-inflammatory effects in cases with complications such as myocarditis, hemolytic anemia, neurological symptoms, hemophagocytic lymphohistiocytosis, respiratory distress and severe splenomegaly stridor. However, there is no universal standard for their use in uncomplicated cases (7).

Acyclovir is a nucleoside analogue with high in vitro antiviral activity (8). Good justification is needed to ensure proper results when using antiviral drugs, but so far, there has been no agreement on the effectiveness of antiviral drugs in treating infectious mononucleosis (9). Therefore, the present study was conducted to evaluate the therapeutic effect of oral acyclovir in children with infectious mononucleosis admitted to the Taleghani Hospital in Gorgan, Iran.

MATERIALS AND METHODS

This randomized double-blind clinical trial was performed on 48 patients with infectious mononucleosis admitted to to the Taleghani Hospital in Gorgan (Iran) in 2020. The samples size was calculated according to the study of Jessica E. Yager et al. (10) with a power of 90% ($\alpha = 0.05$, $p_1 = 17.8$ and $p_2 = 61.3$) and considering a drop-out rate of 10%. Inclusion criteria included age of 1-16 years, having recent symptomatic infectious mononucleosis (sore throat, lymphadenopathy and fatigue), fever of no less than 38 °C and clinical signs and laboratory findings favoring the disease (11). Patients with mild symptoms, severe underlying disease, renal impairment (serum creatinine >1.6 mg/dl) and a streptococcal sore throat as well as those under steroid or antiviral therapy in the last two weeks were excluded from the study. Eligible patients were then randomly divided into an intervention (n=22) and a control (n=26) group by the Four Blocks framework.

This was a double-blind, randomized, interventional clinical trial. The intervention

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group received 80 mg/kg/day oral acyclovir q.i.d. for five days and the control group received placebo (Starch capsule, Barij Essence). In both groups, fluid therapy was performed in case of oral food intolerance, and oxygen therapy was performed in patients with moderate to severe stridor.

In case of confirmed co-infection, clindamycin was administered at a dose of 40 mg/kg/day divided q8h, and in case of severe stridor, max 60 mg/kg/day prednisolone was administered for one to seven days and then tapered after seven days. In case of fever, acetaminophen was administered to patients at a dose of 10-15 mg/kg for a maximum of five doses per 24 hours. Other patients were treated with the same regimen. Patients were visited daily and if their clinical symptoms (e.g. fever, stridor, sore throat, and oral tolerance) improved for 48 hours, the treatment was considered over. After discharge, patients were visited on an outpatient basis once a week until symptoms subsided; follow up continued for up to one month after the treatment initiation. The rate of response to treatment was measured based on the opinion of a pediatric infectious disease subspecialist and a checklist for the severity of the disease designed by Tynell et al. (11). The main outcome included a reduction in the course of treatment and the severity of the disease, and reduction in corticosteroid therapy was considered a minor outcome. Demographic information and the main variables of the study were recorded using a checklist.

During the study, patients' blood pressure, heart rate and temperature were checked every four hours. Side effects including fever (above 38 °C), chills, sweating, hot flashes, nausea, vomiting, high blood pressure, headache and dizziness, stomachache and bleeding were also recorded.

According to several studies, the dose used in the present study was completely safe and secure (12, 13); however, some mild side effects such as headache, nausea, diarrhea, drowsiness, etc. may occur. All patients were under the direct supervision of a physician at the time of drug administration. Any possible side effects were monitored, and in case of serious side effects (although very rare), the drug was discontinued and standard treatment was started. Patients and their guardians were free to withdraw from the study anytime.

Data were described as mean ± standard deviation. Normality of data was assessed using the Shapiro-Wilk test. The t-test was used for analysis of normal data and its non-parametric equivalent, i.e. the Mann-Whitney test was used to measure the recovery time in the two groups for non-normal data. The chi-square test was used to evaluate the symptoms of the disease in both groups. All statistical analyses were carried out in SPSS 18 and at significance level of ≤0.05.

RESULTS

The mean age of patients was 6.36 ± 3.20 years. As shown in (table 1), there was no significant difference between the two groups in terms of gender, mean age and weight of patients.

Table 1. Demographic characteristics of the subjects

Variables		Intervention group (N=22)	Control group (N=26)	P-value
Gender (N, %)	Male	10 (45.46%)	13 (50%)	0.82
	Female	12 (54.54%)	13 (50%)	
Age (years)		5.66±2.82	6.93±3.43	0.503
Weight (kg)		22.01±10.39	23.38±11.52	0.215

The chi-squared or Mann-Whitney test was used to compare the two groups

All subjects were carefully examined by the physician and detailed history was taken from patients or their family members. The results obtained are shown in (table 2).

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Table 2. Evaluation of symptoms and clinical findings of patients in each group

Signs or symptoms		Intervention group	Control group	P-value
		Frequency (%)	Frequency (%)	
Nausea and vomiting	Yes	5 (22.7%)	5 (19.2 %)	0.531
	No	17 (77.3%)	21(80.8%)	
Oral food intolerance	Yes	5 (22.7%)	5(19.2%)	0.521
	No	17 (77.3%)	21(80.8 %)	
Distress	Yes	5 (22.7%)	6(23.1%)	0.625
	No	17 (7.3%)	20(76.9%)	
Fever	Yes	21 (95.5%)	24(92.3%)	0.545
	No	1 (4.5%)	2(7.7 %)	
Weight loss	Yes	4 (18.2%)	3(11.5%)	0.403
	No	18 (81.8%)	23(88.5%)	
Exudative erythema	Yes	19 (86.4%)	20(76.9%)	0.234
	No	3 (13.6%)	6(23.15%)	
Lymph node tenderness	Yes	3 (13.6%)	5(19.2%)	0.452
	No	19 (86.4%)	21(80.8%)	
Hepatomegaly	Yes	0 (0%)	2(7.7%)	0.288
	No	22 (100%)	24(92.3 %)	
Splenomegaly	Yes	11 (50%)	9(34.6%)	0.217
	No	11 (50%)	17(65.4%)	
Rash	Yes	0 (0%)	2(7.7%)	0.288
	No	22 (100%)	24(92.3%)	
Overall condition	Good	15(68.2%)	15(57.7%)	0.759
	Not Good	5(22.7%)	8(30.8%)	
	Bad	2(9.1%)	3(11.5%)	
Mental status	Normal	16(72.7%)	16(61.5%)	0.523
	Low Depressed	6(27.3%)	8(30.8%)	
	Depressed	0(0%)	2(7.7%)	
Sore throat	Mild	4(18.2%)	9(34.7%)	0.054
	Moderate	13(60%)	15(57.7%)	
	Severe	5(22.8%)	2(7.6%)	
Swallowing difficulty	Solid	5(19.2%)	3(13.6%)	0.938
	Liquid	2(7.7%)	1(4.5%)	
	Saliva	1(3.8%)	1(4.5%)	
	None	14(63.3)	22(84.6%)	
Tonsil swelling	Mild	3(13.6%)	5(19.2%)	0.872
	Moderate	17(77.3%)	18(69.2%)	
	Severe	2(9.1%)	3(11.6%)	
Lymphadenopathy Region	Cervical	17(77.2%)	22(84.6%)	0.863
	Submandibular	3(13.6%)	4(15.4%)	
	Sublingual	2(9.1%)	0(0%)	

*The chi-square test was used to compare the two groups.

Other variables including sleep problems, headache, night sweating and school absence did not differ between the two groups (Table 3).

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Table 3. Sign and symptoms of infectious mononucleosis in the intervention and the control groups

Sign or symptom		Intervention	Control	P-value
		Frequency (%)	Frequency (%)	
Sleep Problem	Yes	5(22.7%)	9(34.6%)	0.281
	No	17(77.3%)	17(65.4%)	
Headache	Yes	0(0%)	3(11.5%)	0.151
	No	22(100%)	23(88.5%)	
Night Sweating	Yes	1(4.5%)	2(7.7%)	0.564
	No	21(95.5%)	24(92.3%)	
School Absence	Yes	8(26.4%)	19(73.1%)	1.00
	No	14(63.6%)	7(26.9%)	

*The chi-square test was used to compare the two groups.

DISCUSSION

Early EBV infections with or without clinical manifestations of infectious mononucleosis are associated with several complications that are primarily classified by immune pathological responses to the virus. Among these, autoimmune hemolysis, airway obstruction following tonsil swelling, splenic rupture, encephalitis and myocarditis are observed even in asymptomatic patients. Agranulocytosis, aplastic anemia and other rare but severe features of acute progressive EBV infection occasionally occur in asymptomatic patients and may indicate EBV-specific cellular immunodeficiency. For such cases, special antiviral treatment regimens are required. Acyclovir has specific anti-EBV activity (14). Despite the disappearance of viral shedding during the treatment of acute infectious mononucleosis, several studies have reported no significant effect on the clinical symptoms of the subjects (15, 16). Consistent with the results of these studies, our findings indicated that acyclovir therapy had no significant effect on the clinical symptoms of patients with acute infectious mononucleosis. However, some studies reported that antiviral therapy had a significant effect on the severity of patients' clinical symptoms (10, 17, 18).

In our study. acyclovir therapy had a non-significant impact on reducing the severity of clinical symptoms, length of hospital stay, sore throat, weight loss, etc. In line with our study, Tynell et al. reported that acyclovir significantly reduced virus influx but had no significant effect on the severity of symptoms in the intervention group (11). In another study, Usami et al. reported that acyclovir can reduce the duration of the disease (17). Some other studies reported a heterogeneous pattern (19-21). The divergence in the results of previous studies may be due to differences in the drug dosage, age of subjects, duration of the symptoms, endpoints definition for discharge or end of treatment and patients' susceptibility to virus colonization in the oropharynx. However, most studies concluded that acyclovir therapy can reduce the virus outbreak in patients with infectious mononucleosis. For instance, a previous study reported that oral acyclovir could efficiently inhibit shedding of the virus in the oropharynx (22).

The main limitation of acyclovir is the low absorption rate (10-20%), which can be resolved by the prodrug valaciclovir (23). However, no enhanced antiviral effect by this drug can be expected in comparison with high doses of acyclovir (15). Some studies have reported that penciclovir effectively inhibits EBV replication in vitro and can be considered as an alternative treatment regimen (24). Based on the evidence, the dose of acyclovir used in our study should suppress EBV proliferation. We believe that the clinical ineffectiveness in the present study was due to mechanisms other than the insufficient antiviral effect on infected cells.

In a previous study, acyclovir and valaciclovir therapy for less than two weeks could not control viral replication in the oral

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cavity. Other nucleoside analogues, such as famciclovir or valganciclovir, may exhibit better anti-EBV effects in vivo than valaciclovir and acyclovir, which can be investigated in future clinical trials (25).
In severely ill patients, steroid therapy may prevent primary airway obstruction. A study on 11 patients with severe infectious mononucleosis showed the clinical benefits of this treatment (26).

Given that the results of studies on the effectiveness of acyclovir and similar metabolites in reducing patients' clinical symptoms and duration of treatment are inconclusive, administration of acyclovir and similar metabolites in patients relies on the clinical suspicion of the specialist and the patient's clinical condition.

Study limitations

The main limitation of the study was the time period of the study, which coincided with the COVID-19 pandemic and according to health protocols, the admission rate in the hospital was kept at minimum. Therefore, the study subjects were with strict medical indications. Indeed, the statistical population and clinical condition of the subjects were strongly influenced by the pandemic. Furthermore, most patients' parents were not willing to participate in the study so that the study population did not have an ideal homogeneous distribution.

CONCLUSION

Based on our findings, acyclovir administration in patients with infectious mononucleosis has no significant effect on reduction of disease severity and patients' symptoms. Therefore, the use of acyclovir and similar metabolites in the treatment of patients with infectious mononucleosis depends on the suspicion and clinical evaluation of the specialist, and its routine administration is not recommended for all patients.

DECLARATIONS

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Ethics approvals and consent to participate

The study was approved by the Ethics Committee of Vice-Chancellor for Research and Technology of Golestan University of Medical Sciences (ethical code: IR.GOUMS.1399.345). Moreover, informed consent was obtained from legal guardians of the patients. The study has been registered as a clinical trial under the following registry code: IRCT20201201049554N1.

Conflict of interest

The authors declare that there is no conflict of interest regarding publication of this article

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