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Examining the relationship between the timing of Oseltamivir treatment and clinical indicators, and the duration of hospitalization in children with influenza: A cross-sectional study in Gorgan, Iran

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Abstract

Background: One of the treatment methods used for influenza is the administration of antiviral medications, including oseltamivir. This study aimed to investigate the impact of the timing of oseltamivir treatment on clinical indicators and complications in hospitalized children with influenza.

Methods: This cross-sectional study was conducted on all children diagnosed with influenza who visited Taleghani Hospital in 2024. Demographic information, clinical indicators, including oxygen saturation, fever, general condition, oral intolerance, and disease outcomes such as length of hospital stay and complications were recorded using a researcher-designed checklist. The collected data were entered into SPSS software version 23.

Results: In this study, 134 children with influenza, with a mean age of 63 ± 42 months, were examined. Among them, there were 69 males and 65 females. Fever, cough, and loss of appetite were the most prevalent symptoms, occurring in 83%, 65%, and 62% of the cases, respectively. Sore throat and eye pain were the least common symptoms, reported at 9% and 10%. A total of 87 participants received oseltamivir. The overall recovery rate was 74% in the entire study population, as well as among those who received oseltamivir, and only one death was observed.

Conclusion: Based on the results, early treatment with oseltamivir has been effective in reducing clinical symptoms of influenza in affected children. Therefore, it is advisable to initiate treatment with this medication promptly upon the admission of sick children to the hospital.

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Highlights

What is current knowledge?

There are several options for treating influenza-like infections, including antiviral treatments, monoclonal antibodies, corticosteroids, antibiotics, antifungals, and supportive measures, the varying results of studies regarding the effectiveness of the timing of oseltamivir administration on the outcomes of influenza in children.

What is new here?

Based on the results, early treatment with oseltamivir has been effective in reducing clinical symptoms of influenza in children. It is recommended that treatment with this medication be started as soon as the children are admitted to the hospital. Therefore, it is advisable to initiate treatment with this medication promptly upon the admission of sick children to the hospital.

Introduction

Influenza is a respiratory infection caused by a negative-sense RNA virus from the Orthomyxoviridae family. Three distinct types of influenza viruses infect humans, including types A, B, and C. Type A influenza involves several species, including humans, pigs, horses, and birds. Each subtype of type A virus is identified by the numbering of its hemagglutinin and neuraminidase proteins (Such as H3N2 and H5N1) (1,2). Type B influenza is classified based on its lineages. The circulating lineages include Yamagata (B/Y) and Victoria (B/V) (3).

Every year, seasonal influenza affects one billion people worldwide, resulting in up to five million severe cases and nearly half a million recorded deaths (4,5). Seasonal influenza outbreaks can impact all age groups, leading to severe illness or death, particularly in high-risk individuals such as adults over 35 and children under two. It is estimated that influenza accounts for three to five million cases of severe illness and approximately 290,000 to 650,000 deaths annually (6,7).

There are several options for treating influenza-like infections, including antiviral treatments, monoclonal antibodies, corticosteroids, antibiotics, antifungals, and supportive measures (8). Oseltamivir is an antiviral medication used to treat influenza A and B. It works by inhibiting the viral neuraminidase necessary for virus replication (9). According to the CDC, oseltamivir phosphate cannot be used as a substitute for vaccination in preventing influenza. However, it is the only antiviral medication approved and recommended for influenza in young infants (10). Treatment with oseltamivir should begin within two days of illness onset. However, oseltamivir is the most effective and efficient when treatment starts as soon as possible after the onset of symptoms (11). There have been no reported clinical symptoms related to adverse reactions from oseltamivir (12). Treatment with oseltamivir should not be delayed due to diagnostic tests or rapid influenza identification tests (13). Research has shown that oseltamivir is an effective treatment for reducing complications and the duration of hospitalization in children with influenza (14).

Given the importance of oseltamivir in the treatment of influenza in children and the varying results of studies regarding the effectiveness of the timing of oseltamivir administration on the outcomes of influenza in children, this study was conducted to investigate the effect of the timing of oseltamivir treatment on clinical indicators and the duration of hospitalization in children hospitalized with influenza.

Methods

Study design

In this cross-sectional study, all children with influenza who visited Taleghani Hospital in Gorgan in the year 2024 and met the eligibility criteria for the study were examined. The samples studied were selected through convenience sampling.

Data collection

Information was gathered using a demographic information form that included age, gender, medical history, hospitalization history, and contact history with an infected individual. Additionally, clinical indicators such as respiratory rate, oxygen saturation, heart rate, fever, general condition, appetite, severity of respiratory distress, and duration of hospitalization were collected using a checklist designed based on available information. The diagnosis of influenza in all children visiting the emergency department or clinic of Taleghani Hospital is based on the patient's clinical symptoms and confirmed through PCR testing and virology tests. Symptoms of influenza include fever, chills, cough, difficulty breathing, fatigue, sore throat, runny nose, myalgia, body aches, headache, and in some cases, gastrointestinal symptoms such as diarrhea, vomiting, and abdominal pain. Along with testing for the influenza virus, a test for COVID-19 was also conducted, and only those who tested negative were included in the study. The speed of clinical symptom improvement and response to supportive treatment in patients being treated with oseltamivir should be examined.

The inclusion criteria were having the flu and not having any malignant diseases or immune system deficiencies. The exclusion criteria were discharge with the patient's consent and the patient's death.

Statistical analysis

After collection, the data were entered into SPSS software version 23. Descriptive statistics, including mean and standard deviation (SD), as well as frequency distribution tables (Frequency - percentage), were used to describe quantitative variables. The Shapiro-Wilk test was employed to assess the normality of the data. Independent t-test, or the non-parametric Mann-Whitney U test was used to compare the means of quantitative variables between two independent groups. ANOVA or Kruskal-Wallis tests, along with Post Hoc analyses, were applied to compare the means of variables among more than two groups. Chi-square test or Fisher's exact test was utilized to analyze nominal and ordinal qualitative variables in two independent groups. A p-value of less than 0.05 was considered statistically significant.

Results

In this study, 134 children aged between three and 160 months with influenza were examined. Among them, 69 (51%) were male and 65 (48.5%) were female. The analysis of influenza symptoms revealed that fever, cough, and loss of appetite were the most commonly reported symptoms among the patients (83%, 65%, and 62%, respectively). Additionally, 62 patients (46%) exhibited more than one symptom of the illness concurrently. Sore throat and eye pain were the symptoms with the lowest prevalence (9% and 10%, respectively). Furthermore, half of the patients (51%) had a history of contact with an individual or individuals infected with influenza (Table 1).

The study results indicated that 87 out of 134 children diagnosed with influenza had taken oseltamivir. The same number reported a history of using other medications prior to their hospital visit. All patients who received oseltamivir showed tolerance to the drug. The treatment outcome was recovery in 74% of the patients, and there were no fatalities except for one case.

According to Figure 1, there was a significant relationship between the day treatment with oseltamivir began and the length of hospital stay ($p < 0.001$). The average length of hospital stay was three days for patients who started oseltamivir on the first day, while it was 9.1 days for those who started on the fifth day.

The prevalence of all clinical symptoms observed from the first to the fifth day of oseltamivir use showed a significant difference ($p < 0.001$). Only the prevalence of runny nose did not show a significant difference over the five-day course of oseltamivir ($p=0.058$). In all cases, the clinical signs in individuals with positive clinical symptoms were more prevalent on the fifth day compared to other days, except for cough, which had a similar prevalence on both the third and fifth days. Nevertheless, the number of individuals who were asymptomatic on the fifth day was significantly higher than the number of those with clinical symptoms. Although the treatment outcome at five days of oseltamivir use did not show a significant difference ($p=0.076$), the number of individuals who experienced improvement was higher than on other days (27 individuals) (Table 2).

According to Table 3, on the first day of oseltamivir use, the number of improved females and males was equal. However, from the second day to the fifth day, except for the fourth day, the number of males significantly exceeded that of girls ($p < 0.001$). The duration of hospitalization was significantly longer for individuals whose treatment extended to the fifth day of oseltamivir use ($p < 0.001$). In individuals who showed improvement from the second day onward, the arterial oxygen saturation levels were significantly higher ($p < 0.001$).

Table 1. Frequency distribution of children with influenza based on clinical symptoms associated with influenza

Demographic and clinical variables	Mean	Standard deviation
Age (Month)	63.3	14.2
Weight (Kg)	18.2	11.1
Duration of hospitalization (Days)	5.08	4.3
Duration of oseltamivir administration (Days)	3.2	1.3
Arterial blood oxygen saturation level (Percentage)	97.5	14.5
Body temperature (Celsius)	38.6	9.6
Onset of symptoms (Days)	6.5	2.5
Clinical symptoms	Yes N (%)	No N (%)
Sore throat	13 (9.7)	1212 (90.3)
Fever	112 (83.5)	22 (16.5)
Vomiting	38 (28.3)	96 (71.7)
Weakness and fatigue	34 (25.3)	100 (74.7)
Having more than two symptoms of illness	62 (46.2)	72 (53.8)
Underlying health condition	42 (31.3)	92 (68.7)
History of contact	69 (51.4)	65 (48.6)
Appetite	50 (37.3)	84 (62.7)
Muscle involvement	41 (30.6)	93 (69.4)
Cough	88 (65.6)	46 (34.4)
Diarrhea and gastrointestinal symptoms	45 (35.5)	89 (66.5)
Simple congestion - respiratory symptoms	32 (23.8)	102 (76.2)
Runny nose	41 (30.3)	93 (69.7)
Eye pain	14 (10.4)	120 (89.6)
Other cases	19 (14.1)	115 (85.9)

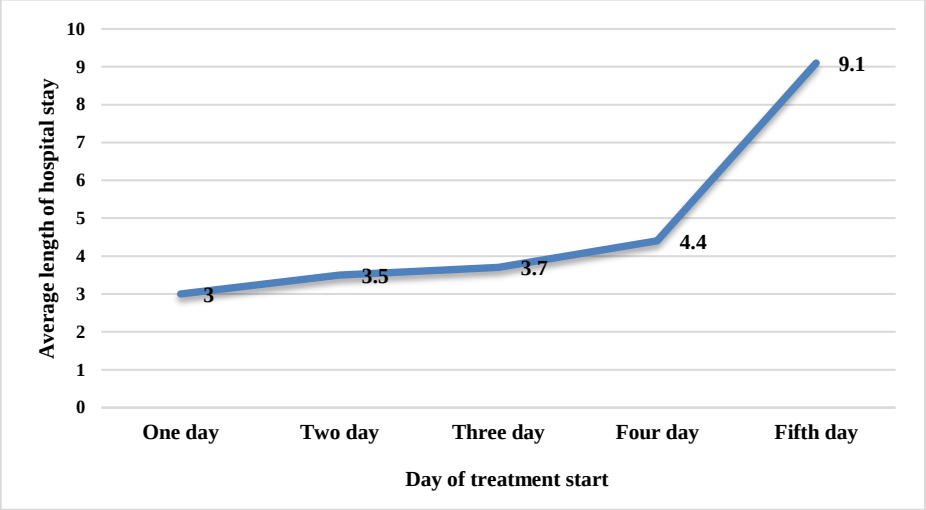

Figure 1. The relationship between the start date of treatment with oseltamivir and the duration of hospital stay for patients

Table 2. The relationship between clinical symptoms of influenza and outcomes with days of Oseltamivir use

Variables N (%)		Days of Oseltamivir use					
		One	Two	Three	Four	Five	P-value
Muscle tension	Yes	2 (25)	6 (40)	7 (25)	2 (40)	9 (29)	< 0.001
	No	6 (75)	9 (60)	21 (75)	3 (60)	22 (71)	
Coughing	Yes	4 (50)	11 (73)	18 (64)	3 (60)	18 (58)	< 0.001
	No	4 (50)	4 (26)	10 (35)	2 (40)	13 (42)	
Diarrhea and gastrointestinal symptoms	Yes	3 (37)	4 (26)	5 (17)	2 (40)	11 (35)	< 0.001
	No	5 (62)	11 (73)	23 (83)	3 (60)	20 (64)	
Mild cramping - respiratory symptoms	Yes	1 (12)	3 (20)	5 (17)	1 (20)	7 (22)	< 0.001
	No	7 (87)	12 (80)	23 (82)	4 (80)	24 (77)	
Runny nose	Yes	3 (73)	2 (13)	14 (50)	0 (0)	9 (29)	0.058
	No	5 (62)	13 (83)	14 (50)	5 (100)	22 (71)	
Eye pain	Yes	1 (12)	0 (0)	2 (7)	1 (20)	5 (16)	< 0.001
	No	7 (87)	15 (100)	26 (93)	4 (80)	26 (83)	
Desire	Yes	3 (37)	7 (46)	11 (39)	4 (80)	12 (38)	< 0.001
	No	5 (63)	8 (53)	17 (60)	1 (20)	19 (61)	
Drug delivery	Yes	6 (100)	14 (100)	27 (100)	5 (100)	30 (96.8)	< 0.001
	No	0 (0)	0 (0)	0 (0)	0 (0)	1 (3.2)	
Outcome	Improvement	3 (37)	11 (67)	16 (67)	4 (80)	27 (87)	0.076
	Relative improvement	0 (0)	2 (10)	3 (10)	0 (0)	2 (6)	
	Death	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)	
	Discharge with patient consent	5 (63)	2 (13)	6 (21)	1 (20)	1 (3)	

Table 3. The relationship between demographic and clinical variables and days of Oseltamivir use

Variables		Days of Oseltamivir use					
		One	Two	Three	Four	Five	P-value
Sex N (%)	Male	4 (50)	6 (60)	15 (53)	1 (20)	18 (58)	< 0.001
	Female	4 (50)	6 (40)	13 (47)	4 (80)	13 (41)	
Duration of hospitalization (Mean±SD)		3 ±1	3.5 ± 1.1	3.7 ± 1.2	4.4 ± 1.3	9.1 ± 3.2	< 0.001
Arterial blood oxygen saturation level (Mean±SD)		96.3 ± 21.3	98.2 ± 18.4	97.2 ± 20.4	98.6 ± 17.3	97.1 ± 19.3	< 0.001

Discussion

The results of this study showed that fever, cough, and loss of appetite had the highest prevalence, while sore throat and eye pain had the lowest prevalence. Eighty-seven people received oseltamivir, and the treatment outcome was a 74% recovery rate in the overall study population, as well as among those who received oseltamivir, with only one death observed. The prevalence of disease-related clinical symptoms, except for runny nose, was significantly higher on the fifth day compared to previous days. However, on the other hand, there was a significant decrease in the frequency of clinical symptoms by the fifth day.

In a meta-analysis study in 2018 years, Malosh et al. demonstrated, using five randomized controlled and placebo trials, that early treatment with oseltamivir (Starting treatment from the second day of clinical symptoms) is effective for influenza (15). This finding was also observed and confirmed in the results of our study. In a study conducted in the United States and Canada in 2001, Whitley et al. examined the oral treatment of oseltamivir in children with influenza. They reported that the effectiveness of the treatment depended on the reduction or elimination of cough, reduction or elimination of cold symptoms, normalization of body temperature, return to previous activities, and overall well-being. This clinical trial focused on children aged 1-2 years. They compared the oseltamivir group with the placebo group and demonstrated that the duration of illness in children receiving oseltamivir was significantly shorter than in the placebo group. Treatment with oseltamivir reduced symptoms such as runny nose, cough, and fever, and the diagnosis of otitis media in children was lower compared to the placebo group (12% versus 21%). The use of antibiotics was significantly lower in the group receiving oseltamivir compared to the placebo group. However, contrary to the results of our study, the tolerance for oseltamivir was lower, with only 41% of patients receiving oseltamivir showing drug tolerance (16). In our study, 99% of the patients showed drug tolerance, which was noteworthy.

Research has shown that although treating influenza with oseltamivir reduces the duration of the illness and the severity of symptoms in children, findings from another study indicate that prescribing antiviral treatment based solely on clinical diagnosis may lead to poor treatment outcomes in children (15). In the study by Heinonen et al., children aged 1-3 years with respiratory infections were examined. During each visit, a nasal swab sample was taken to diagnose influenza, and the doctor recorded their opinion on whether the child had influenza. Among 2,288 infections, the overall sensitivity of clinical diagnosis for influenza was 38%, and the positive predictive value was 32%. Children diagnosed with influenza received oral oseltamivir treatment. A total of 408 children with influenza were divided into two groups: one receiving oseltamivir and the other a placebo. Within the first 24 hours of medication, no significant or noticeable reduction in symptoms was observed. Treatment for patients with influenza A began 24 hours after onset. In children with influenza A, symptoms were reduced on average within four days after starting treatment, which was consistent with the results of our study. However, the effectiveness of the medication in reducing symptoms was not observed in patients with influenza B (17).

Walsh et al. have also reported that early use of oseltamivir in hospitalized children was associated with a shorter hospital stay and a lower chance of readmission within seven days, transfer to the ICU, use of ECMO, and death (18). This study, in terms of the age range of children with influenza examined, was similar to our study and highlighted the accelerated effect of oseltamivir treatment in reducing mortality. In our study, there was a significant and strong reduction in mortality, with only one death observed. However, it should be noted that their study had a much larger sample size compared to ours.

In a more recent study, Qin et al. in 2022 examined the clinical effectiveness of oseltamivir in children with different subtypes of influenza infections in China. Their findings indicated that treatment with oseltamivir did not significantly shorten the duration of fever and was not a good or prominent relief for flu-like symptoms in these patients. In this study, 998 children with acute respiratory infections were registered and divided into groups with influenza A virus infection, influenza B virus infection, both A and B infections and those without influenza infection. The average age of the patients was 4.82 ± 2.73 years (19). This result is contrary to the findings of the present study, and the reason for this could be due to genetic and environmental differences between the two studies, as well as variations in healthcare and treatment systems in the two countries. However, the average age of patients in the research by Qin et al. was approximately close to the average age of patients in our study (25.5 ± 3.5 years) and was only slightly lower.

Although we did not examine the economic benefits of early use of oseltamivir for patients in this study, it can be helpful to consider previous studies conducted in this area. For instance, Lim et al. (2015) investigated the economic advantages of timely treatment with oseltamivir in 116 children under 15 years old hospitalized with influenza in South Korea. The study results indicated that a delay in starting treatment with oseltamivir was associated with increased hospital treatment costs for patients hospitalized with influenza. Specifically, the costs for patients who began oseltamivir treatment less than three days after admission were 60.84% higher than those who started immediately upon admission (20). One of the strengths of this study was examining the effect of oseltamivir on various clinical symptoms, and one of its limitations was the lack of recorded information for some patients.

Conclusion

Based on the findings, early treatment with oseltamivir effectively reduced clinical symptoms of influenza in children. It is recommended that treatment with this medication be started as soon as the children are admitted to the hospital. Therefore, it is advisable to initiate treatment with this medication promptly upon the admission of sick children to the hospital. It is recommended that future studies investigate the effects of the drug oseltamivir in treating and reducing the symptoms and complications of influenza in children, based on the different types of influenza A and B.

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Ethical statement

The research followed the tenets of the Declaration of Helsinki. The Ethics Committee of Golestan University of Medical Sciences approved this study (Ethical code: IR.GOUMS.REC.1403.165). Accordingly, written informed consent was taken from all participants. Additionally, ethical issues (Including plagiarism, data fabrication, and double publication) were completely applied by the authors.

Conflicts of interest

The authors declare no conflict of interest.

Author contributions

JP: Conceptualization, project administration, and writing. MGG: Conceptualization, methodology, investigation, software, and visualization. AK: Investigation and writing. JP: Conceptualization and validation. All authors read and approved the final manuscript.

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