Open Forum Infectious Diseases

MAJOR ARTICLE

Clinical Effectiveness of Intravenous Peramivir Compared With Oseltamivir in Patients With Severe Influenza A With Primary Viral Pneumonia: A Randomized Controlled Study

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Background. High-quality evidence confirms that the clinical efficacy of peramivir in severe influenza patients with primary viral pneumonia is lacking. To optimize clinical medication, we evaluate the different efficacy between peramivir and oseltamivir in the treatment of severe influenza A with primary viral pneumonia.

Methods. A single-center, randomized, controlled trial was conducted during the Chinese influenza season from December 2018 to April 2019 in patients with severe influenza A with primary viral pneumonia. A total of 40 inpatients were enrolled and treated with either intravenous peramivir (300 mg, once daily for 5 days) or oral oseltamivir (75 mg, twice daily for 5 days).

Results. The duration of influenza virus nucleic acid positivity in the oseltamivir group and the peramivir group was 2.95 days and 2.80 days, respectively. The remission times of clinical symptoms in the oseltamivir group and the peramivir group were 3.90 days and 3.25 days, respectively. In addition, the remission time of cough symptoms in the peramivir group (63.89 hours) was shorter than that in the oseltamivir group (75.53 hours). There was no significant difference between these values ($P > .05$). The remission time of fever symptoms in the oseltamivir group was 23.67 hours, which was significantly longer than that in the peramivir group (12.32 hours) ($P = .034$).

Conclusions. Peramivir is no less effective than oseltamivir in the treatment of severe influenza A with primary viral pneumonia, and patients treated with peramivir had significantly shorter remission times of fever symptoms than those treated with oseltamivir.

Keywords. influenza A; oseltamivir; peramivir; pneumonia.

Influenza is an acute respiratory disease caused by influenza virus, which has the characteristics of rapid transmission and strong infectivity. In a typical influenza season, influenza viruses can cause infection in 5%–10% of the population. According to the World Health Organization's Global Burden of Disease Study, influenza viruses currently cause more than 650 000 deaths worldwide. The global epidemic of influenza has caused serious public health and economic problems [1–4]. In recent years, successive outbreaks of influenza in China have led to a large number of severe cases and even deaths. Influenza is a self-limited disease in the absence of complications. The most common clinical features are fever, cough, headache, muscle ache, general discomfort, etc. However, some patients, such as the elderly, young children, obese people, pregnant women, and individuals with chronic underlying diseases, or even the general population, may develop a severe case due to the occurrence of complications, such as pneumonia, nervous system injury, and cardiac injury. A small number of critically ill patients progress rapidly and die from these complications [5–7]. In fact, influenza is usually accompanied by primary viral pneumonia. Therefore, an increasing number of scholars have recently focused on the study of severe influenza combined with primary viral pneumonia [8].

According to the influenza diagnosis and treatment program (2019 edition) issued by the National Health Commission of the People's Republic of China, the 3 classes of anti-influenza drugs currently on the market in China are M2 proton channel blockers, hemagglutinin inhibitors, and neuraminidase inhibitors. The representative M2 proton channel blockers are amantadine and rimantadine. However, M2 ion channel blockers are effective only for influenza A, and all influenza A strains are resistant to older drugs, so those drugs are no longer recommended. The representative hemagglutinin inhibitor is abidol. However, its

Received 9 July 2020; editorial decision 10 November 2020; accepted 12 November 2020.

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Open Forum Infectious Diseases®2020

DOI: 10.1093/ofid/ofaa562

clinical application is limited in China, so its efficacy and adverse reactions need further attention [9–13]. At present, neuraminidase inhibitors are the most widely used anti-influenza drugs. Representative neuraminidase inhibitors include oseltamivir, zanamivir, and peramivir. Neuraminidase, also known as sialidase, is a glycoprotein on the surface of influenza virus that can catalyze the hydrolysis of glycosidic bonds between the end of sialic acid and adjacent oligosaccharides, promoting detachment of mature influenza virions from host cells to allow infection of new cells and eventually leading to the spread of the virus in the human body. Neuraminidase inhibitors selectively inhibit neuraminidase, thereby affecting viral replication and spread [14, 15]. The neuraminidase inhibitors currently on the market include oseltamivir phosphate capsules, oseltamivir phosphate granules, zanamivir inhalation powder aerosol, and peramivir sodium chloride injection. Oseltamivir is an oral preparation, and zanamivir is an inhalant that is not convenient for severe patients. In 2009, the marketing of peramivir sodium chloride injection created a convenient method of administration for severe and critical influenza patients [16].

Peramivir is a cyclopentane derivative containing a guanidine group and a lipophilic side chain [17, 18]. As a novel intravenously administered anti-influenza drug, peramivir has a plasma half-life of 6–8 hours and a high blood concentration, and it can bind to 3 sites on the amino acid residues of the neuraminidase active site; thus, peramivir is a fast-acting, long-lasting, potent anti-influenza drug [19–21]. In fact, there are many domestic and international studies verifying the effectiveness of peramivir. For example, the results of cell experiments and animal experiments established by Boltz et al [22] showed that peramivir had a strong inhibitory effect on influenza virus strains and that parenteral administration of peramivir could improve the survival rates of animals. Since then, phase I–III clinical studies conducted in the United States have confirmed that intravenous peramivir treatment has strong inhibitory activity against influenza virus and better efficacy than oral oseltamivir [23]. The Japanese study by Komeda et al [24] collected data from 1309 influenza patients using peramivir between 2010 and 2012 to evaluate the clinical efficacy of peramivir. This trial concluded that the median time for peramivir in treating influenza to relieve influenza symptoms and fever was 3 days, and the efficacy of peramivir in treating influenza was good. However, there are no reports on the effectiveness of peramivir in the treatment of severe influenza complicated with primary viral pneumonia domestically or globally. Animal studies conducted by Tanaka et al [25] in 2015 demonstrated effective treatment of secondary pneumococcal pneumonia established with lethal viruses and influenza viruses by intravenous peramivir infection. However, high-quality evidence from randomized, controlled clinical trials to confirm the clinical efficacy of peramivir in severe influenza patients with primary viral pneumonia is lacking.

This study provides comparative data on the use of different neuraminidase inhibitors in the treatment of severe influenza patients with primary viral pneumonia. We assessed the duration of influenza virus nucleic acid positivity (primary indicator), time to remission of clinical symptoms (primary indicator), time to remission of fever symptoms (secondary indicator), and time to remission of cough symptoms (secondary indicator). The aim of this study was to prove that peramivir was not less effective than oseltamivir in the treatment of severe influenza complicated with primary viral pneumonia.

METHODS AND PATIENTS

Diagnostic Criteria

Our study was a randomized, controlled clinical trial and was conducted in accordance with the ethical standards of the Helsinki Declaration (1964, amended most recently in 2008) of the World Medical Association. This research was approved by the Ethics Committee of the Affiliated Suqian Hospital of Xuzhou Medical University. All participants gave their written informed consent. A clinical research registration number was awarded by the China Clinical Trial Registration Center (ChiCTR1900021135). During the Chinese influenza season from December 2018 to April 2019, this study was performed at the Affiliated Suqian Hospital of Xuzhou Medical University. The patients enrolled in this study were diagnosed with severe influenza A with primary viral pneumonia, which met the diagnostic criteria for the 2019 version of the "Influenza Diagnosis and Treatment Program." First, throat swabs were collected for all patients for reverse-transcription polymerase chain reaction. The results showed that the patients were positive for influenza A virus. Second, imaging examination of a patient showed a ground-glass shadow and patch shadow in the lungs, and the patient's sputum culture showed no bacterial growth or only viridans streptococcus and a C-reactive protein level <20 mg/L. Third, according to the 2019 version of the "Influenza Diagnosis and Treatment Plan," one of the following symptoms indicates a severe case: (1) persistent high fever >3 days, accompanied by severe cough, purulent sputum, bloody sputum, or chest pain; (2) fast breathing frequency, difficulty breathing, and cyanosis of the lips; (3) neurological changes, eg, slow response, lethargy, restlessness, convulsions, etc; (4) severe vomiting, diarrhea, and dehydration; (5) combination with pneumonia; (6) significant worsening of original underlying diseases; and (7) other clinical conditions requiring hospitalization. The patients enrolled in this study had primary viral pneumonia, which met the severe criteria defined in the "Influenza Diagnosis and Treatment Program." Satisfying the above 3 conditions at the same time results in diagnosis of severe influenza A with primary viral pneumonia.

Patients and Groups

The target number of patients with severe influenza A with primary viral pneumonia was 22 based on the result demonstrating noninferiority of intravenous peramivir compared with oseltamivir in influenza patients [26]. Considering that the study period was an influenza epidemic with a large number of patients, the sample size was finally set at 40. A total of 40 patients were included in this study. The inclusion criteria were as follows: (1) confirmed severe influenza A combined with primary viral pneumonia; (2) aged ≥18 years; and (3) the time from the onset of influenza symptoms to the start of treatment administration was within 48 hours. The exclusion criteria were as follows: (1) exclusion of bacterial, fungal, and atypical pathogen infections; (2) vaccination against influenza within 6 months and administration of M2 ion channel blockers and neuraminidase inhibitors within 1 month; and (3) allergy to neuraminidase inhibitors. In this study, SPSS 21.0 software was used to generate random numbers, and participants were randomly divided into peramivir and oseltamivir groups according to the results.

Patient Consent Statement

All participants in this study gave their written informed consent.

Dosing Regimen

The patients in the peramivir group received intravenous infusion of 300 mg of peramivir sodium chloride injection (Ranbaxy, Guangzhou China) once a day, and critical patients could receive 600 mg each time. The course of treatment was 5 days. The course of treatment for severe patients could be appropriately extended. The patients in the oseltamivir group were given 75 mg oseltamivir capsules (Roche, Switzerland) twice daily. The course of treatment was 5 days. The course of treatment for severe patients could be appropriately extended.

Evaluation Indicators

A doctor recorded each patient's basic information (including name, sex, age, etc) and recorded the remission of influenza symptoms (including fever, cough, etc) in detail 3 times a day. Pharyngeal swabs were collected daily after the patients were enrolled, and the time and results were recorded by the doctor. A nurse measured each patient's temperature every 4 hours using a mercury thermometer and recorded it. All information must be registered daily until the patient was discharged.

The duration of influenza virus nucleic acid positivity refers to a change in the influenza virus nucleic acid result from positive to negative that is maintained for more than 24 hours. The remission time of clinical symptoms refers to whether all influenza symptoms disappear or a patient shows only mild influenza symptoms that remain for more than 24 hours. Fever relief refers to the temperature dropping to 37.5°C and remaining constant for more than 24 hours, whereas cough relief refers to no or slight cough that is maintained for more than 24 hours.

Statistical Analysis

The categorical variables in this study are expressed as percentages, and differences between groups were evaluated using the χ^2 test or Fisher's exact test. Measurement data with a normal distribution are expressed as the mean ± standard deviation, measurement data with a nonnormal distribution are expressed as the median (interquartile range). The comparison among groups of continuous variables are tested by Student's *t* test. All data in this study were processed using SPSS 21.0 software, and $P < .05$ was considered significant.

RESULTS

A total of 40 patients diagnosed with severe influenza A with primary viral pneumonia were enrolled in this study between December 2018 and April 2019. Then, they were randomly divided into peramivir and oseltamivir groups of equal size. All patients successfully completed the study (Figure 1). All patients met the inclusion and exclusion criteria, and the first dosing time was within 48 hours of the onset of influenza. The background information of the patients is shown in Table 1. After analysis by the statistical software SPSS, the basic data of the 2 groups of patients were not significantly different.

The clinical efficacies of peramivir and oseltamivir in the treatment of severe influenza A combined with primary pneumonia were evaluated. The main evaluation indicator selected in this study was the duration of influenza virus nucleic acid positivity. The secondary indicators were the remission time of fever symptoms and the remission time of cough symptoms.

If infected with influenza virus, patients will develop fever, headache, muscle ache, fatigue, cough, and other symptoms. In this study, the clinical symptoms of all enrolled patients are shown in Table 2. After the χ^2 test was performed, there were no significant differences in clinical symptoms between the 2 groups. As shown in Table 2, fever and cough were among the top 2 clinical symptoms. Therefore, this study used the remission time of clinical symptoms, the fever symptom relief time, and the cough symptom relief time as secondary indicators to evaluate the clinical efficacy of peramivir in the treatment of patients with severe influenza with primary viral pneumonia.

As shown in Table 3 and Figure 2A, the durations of influenza virus nucleic acid positivity in the oseltamivir group and the peramivir group were 2.95 days and 2.80 days, respectively. A *t* test showed the difference between the 2 groups was not significant ($P > .05$). The remission times of clinical symptoms in the oseltamivir group and the peramivir group were 3.90 days

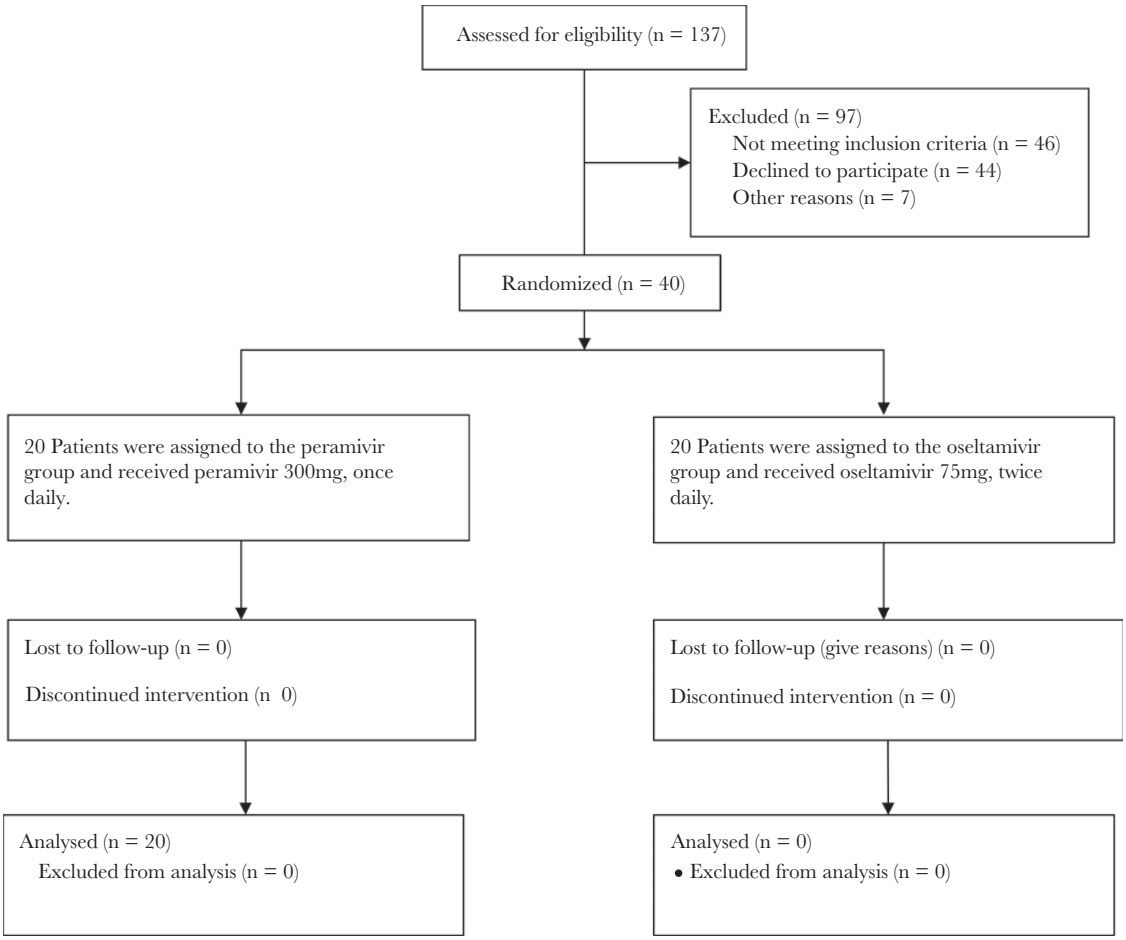

Figure 1. Patient composition.

and 3.25 days, respectively, as shown in Table 3 and Figure 2B. There was also no significant difference between these values ($P > .05$). In addition, the remission time of cough symptoms in the peramivir group (63.89 hours) was shorter than that in the oseltamivir group (75.53 hours). However, the difference between the 2 groups was not significant (Table 3 and Figure 2C).

The remission time of fever symptoms was one of the secondary indicators used to evaluate the clinical efficacies of peramivir and oseltamivir in the treatment of severe influenza A combined with primary pneumonia. Table 3 shows that the remission time of fever symptoms in the oseltamivir group was 23.67 hours, which was significantly longer than that in the peramivir

Table 1. General Characteristics of the Oseltamivir Group and Peramivir Group

Item		Oseltamivir Group	Peramivir Group	*P* Value
Number of patients		20	20	-
Age, years	Mean ± standard deviation	39.00 ± 21.11	33.25 ± 15.22	.46
	Range	18–77	18–85	
Sex	Male/female	8/12	9/11	.75
	%	40/60	45/55	
Maximum body temperature, °C	Mean ± standard deviation	38.67 ± 0.48	38.88 ± 0.77	.35
	Range	37.80–39.40	37.00–39.80	
Virus subtype	Type A H1N1	1	1	1.00
	Type A H3N2	19	19	
	Type B	0	0	
Complication of primary viral pneumonia	Number	20	20	-
Time from onset to administration of drugs (≤48 hours)	Number	20	20	-

Table 2. Clinical Symptoms of the Influenza Patients in the Oseltamivir Group and Peramivir Group

	Oseltamivir Group		Peramivir Group		
Symptom	Number	%	Number	%	*P* Value
Fever	19	0.95	19	0.95	1.00
Cough	16	0.8	19	0.95	.15
Expectoration	14	0.7	12	0.6	.51
Chills	13	0.65	10	0.5	.34
Weakness	6	0.3	5	0.25	.72
Headache	3	0.15	3	0.15	1.00
Muscle soreness	3	0.15	2	0.1	.63
Sore throat	2	0.1	5	0.25	.21
Chest tightness	2	0.1	3	0.15	.63
Coryza	2	0.1	1	0.05	.55

group (12.32 hours) ($P = .034$). As shown in Figure 2D, the proportion of patients with fever in the oseltamivir group after 24, 48, and 72 hours of treatment was 46.67%, 13.33%, and 6.67%, respectively. The proportion of patients with fever after 24, 48, and 72 hours of treatment in the peramivir group was 10.53%, 5.26%, and 0%, respectively. Thus, the proportion of patients with fever after drug treatment was significantly lower in the peramivir group than in the oseltamivir group.

DISCUSSION

Peramivir has achieved good clinical anti-influenza results since it was launched on the market. There have been reports of peramivir administration in the treatment of adults and high-risk groups (including children, the elderly, obese patients, patients with chronic underlying diseases, etc). However, there are few reports on the treatment of severe influenza A with primary viral pneumonia with peramivir. Our study selected a prospective control method to evaluate the clinical efficacy of peramivir in the treatment of severe influenza complicated with primary viral pneumonia. Assessment indicators included the duration of influenza virus nucleic acid positivity, remission time of clinical symptoms, remission time of fever symptoms, and remission time of cough symptoms. After the patients were enrolled, they were treated with peramivir or oseltamivir. The patient's body temperature, respiratory symptoms (such as cough, expectoration, pharyngalgia, and nasal obstruction), and general symptoms (such as general muscle soreness, chills, and fatigue) were recorded 4 times a day. The sampling time and test results of throat swabs were recorded daily. After analyzing the statistical results, it was found that there was no significant difference in the time to conversion to influenza virus negativity between patients taking peramivir and those taking oseltamivir. In a multicenter, randomized, controlled trial conducted by Nakamura et al [5] in 2013, there was no significant difference in the viral titer change in influenza A patients with high-risk factors after administration of peramivir or oseltamivir. This result indicated that the duration of viral positivity was similar in both groups. This result is close to that of our study, which indicates that the ability of peramivir to promote the conversion to influenza virus negativity in severe influenza A patients with primary viral pneumonia is comparable to that of oseltamivir. A phase III, randomized, double-blinded study conducted by Kohno et al [27] in 2011 compared the clinical efficacy of intravenous peramivir with that of oral oseltamivir in the treatment of seasonal influenza. The results showed that the median durations of influenza symptoms were 78.0 and 81.8 hours in the peramivir and oseltamivir groups, respectively. There was no significant difference in the remission time of clinical symptoms between the 2 groups, which was consistent with the results of our study. This suggests that peramivir is equivalent to oseltamivir in improving the clinical symptoms of influenza in patients with severe influenza combined with primary viral pneumonia. In addition, there was no significant difference in the relief time of cough symptoms between the 2 groups after intravenous administration of peramivir or oral administration of oseltamivir in this study, which indicated that the effect of peramivir on improving cough symptoms in severe influenza patients with primary viral pneumonia was not different from that of oseltamivir. A randomized, controlled trial on the cost and effectiveness of peramivir versus those of oseltamivir in the treatment of influenza virus pneumonia in children conducted by Chen et al [28] in 2019 confirmed that patients treated with peramivir had a shorter time to disappearance of their cough symptoms than those treated with oseltamivir. This is different from the results of our study. This may be attributed to the stronger absorption of gastrointestinal drugs in adults than in children, so there was no difference in the time to relieve cough symptoms between intravenous peramivir and oral oseltamivir in this study. Finally, the results of this study showed that the fever remission time (12.32 hours) of patients treated with peramivir was significantly less than that of patients treated with oseltamivir (23.67 hours). According to a meta-analysis by Lee et al [4] in 2017, patients treated with

Table 3. Clinical Efficacies in the Oseltamivir Group and Peramivir Group

	Oseltamivir Group	Peramivir Group	
Item	Mean ± Standard Deviation	Mean ± Standard Deviation	*P* Value
Duration of virus nucleic acid positivity, days	2.95 ± 2.01	2.80 ± 0.95	.76
Remission time of clinical symptoms, days	3.90 ± 2.27	3.25 ± 1.52	.29
Time to fever alleviation, hours	23.67 ± 19.97	12.32 ± 10.39	.034
Time to cough alleviation, hours	75.53 ± 65.65	63.89 ± 37.41	.51

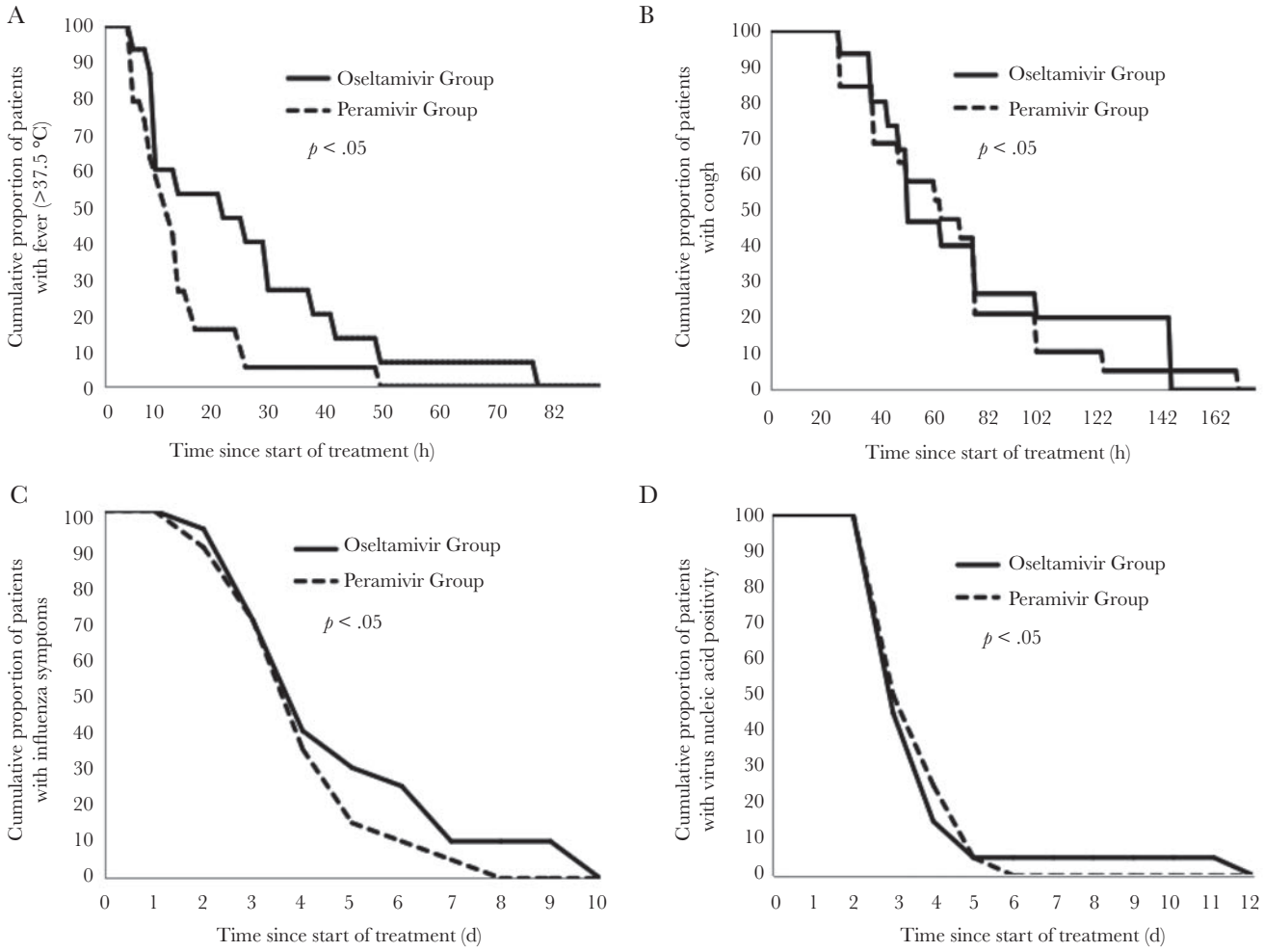

Figure 2. Kaplan-Meier survival curves for the duration of virus nucleic acid positivity (A), remission time of clinical symptoms (B), time to cough alleviation (C), and time to fever alleviation (D) for the oseltamivir and peramivir groups.

intravenous peramivir for influenza had a shorter fever time than those treated with oral oseltamivir treatment. This result is consistent with the results of our study. Therefore, this study indicates that intravenous peramivir can restore the body temperature to normal faster than oral oseltamivir in severe influenza patients with primary viral pneumonia.

In addition, we should recognize the shortcomings of this study. First, the indicators of this study were the duration of influenza virus nucleic acid positivity, the time to clinical symptom remission, the time to fever symptom remission, and the time to cough symptom remission. However, including outcome measures such as mortality, length of hospital stay, or an influenza ordinal recovery scale would be equally as useful in hospitalized patients. Second, this is a single-center study rather than a multicenter study. A total of 40 patients were included in this study, so the sample size was small. This was because the target of this study was severe influenza A combined with primary viral pneumonia, and relatively few patients met the inclusion criteria. So the results of this study may be not equate with that in the true population due to the small sample size. However, only a few clinical prospective, randomized-controlled trials on peramivir for treating severe influenza A with primary viral pneumonia have been published. In addition, a multicenter, large-sample research study is being conducted by our research group. We expect that more meaningful data and results will be obtained.

CONCLUSIONS

In this study, we evaluated the efficacies of peramivir and oseltamivir in the treatment of severe influenza A patients with primary viral pneumonia by comparing the duration of influenza virus nucleic acid positivity, the time to clinical symptom remission, the time to fever symptom remission, and the time to cough symptom remission. There was no significant difference in the durations of influenza virus nucleic acid positivity, the remission times of clinical symptoms, and the remission time of cough symptoms between the oseltamivir group and the peramivir

group. The remission time of fever symptoms in the oseltamivir group was significantly longer than that in the peramivir group. Based on these data, we conclude that peramivir is no less effective than oseltamivir in the treatment of severe influenza A and primary viral pneumonia and that patients who receive peramivir intravenously have significantly shorter remission times of fever symptoms than those treated with oral oseltamivir.

Acknowledgments

We gratefully thank all the participants in the completion of this study.

Financial support. This study was funded by Science and Technology Information Network in Suqian City (No. Z2018188).

Potential conflicts of interests. All authors: no reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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