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Cohort Study

Efficacy of oseltamivir in the treatment of patients infected with Covid-19☆,☆☆

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ABSTRACT

Objective: The recent unprecedented pandemic caused by Sars-Cov-2 (the new coronavirus 2019), is threatening public health around the world. Although several studies have been performed, there is no identified treatment for Covid-19 patients. Here we assessed the efficacy of oseltamivir in combination therapy, by comparing two different therapeutic regimens in hospitalized patients, in improving outcomes and find better treatment for Covid-19 patients.

Methods: This is a single-center retrospective cohort study of 285 confirmed Covid-19 in patients at (XXX). Depending on the date of admission, the patients were divided into two groups; group 1 (oseltamivir group) from February 20, 2020 to March 15, 2020 received Oseltamivir with routine regimen and group 2 (control group) from March 20, 2020 to April 20, 2020 received routine regimen alone that included Azithromycin 500 mg/day and Hydroxychloroquine 200 mg/12 h.

Endpoints including duration of hospitalization, requirement to admission to intensive care unit (ICU) and mechanical ventilation, outcome and mortality rate.

Results: A total of 285 patients were enrolled in the two months, 120 patients for group 1 and 165 for group 2. The median time from admission to discharge was significantly shorter in the oseltamivir group compared to the control group (4.9 vs 6.6 days, $p < 0.001$). Additionally, the mortality rate was found to be lower in the oseltamivir group than in the control group (1.7% vs 6,7%, $p = 0.06$) which was statistically significant by multivariate analysis ($p = 0.03$). The incidence of admission to the ICU (6.7% vs 11.5%, $p = 0.1$) and mechanical ventilation (2.5% vs 4.8%, $p = 0.3$) were also decreased in the oseltamivir group, but was not statistically significant.

Conclusions: This study showed that administration of oseltamivir was associated with shorter length of hospital stay and earlier recovery and discharge of hospital, and a lower mortality rate.

1. Introduction

In late (December) 2019 a new pneumonia with unknown origin, detected in patients who were linked to a seafood wholesale market, where wild animals were illegally sold in China. After testing the samples of the patient's airway epithelial cells, a new coronavirus was detected and described as 2019-nCov, and later named severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) by WHO, and the disease caused by this new virus was named Covid-19 [1].

This new virus is the seventh human coronavirus described to date as responsible for respiratory infections [2], and is classified into the beta coronavirus subgroup [3,4].

☆ This study was conducted in accordance with the declaration of Helsinki and was approved by the Ethics committee of Tehran University of Medical Science (Ethic number: IR.TUMS.MEDICINE.REC.1399.396).☆☆ Written informed consent was obtained from all patients when admitted to the hospital. patients confidentiality was considered by protecting their data and documents.

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Covid-19 rapidly spread in the world and made an unprecedented pandemic on March 12, 2020, became a big concern for global health with threatening public health over the world. Thus there was an urgent need for an effective treatment and conducting clinical trials and studies for assessing the efficacy of different repurposed drugs for treatment and prevention of transmission of this infection [5]. WHO considered Solidarity and a major study, on March 20, 2020 to collect scientific data and compare therapeutic strategies to define effective treatment for patients with Covid-19, wants hospitals overwhelmed by Covid-19 patients to participate, and from physicians to simply record their results as the duration of hospital stay, whether the patients required admission to the intensive care unit (ICU) or ventilation and the day the patient left the hospital or died. "That's all" says Ana Maria Henao Restrepo, a medical officer at WHO's Emergency program [5].

There, we decided to do our duty in this solidarity and describe the result of our therapeutic regimens in this hospital, as a center for Covid-19 patients.

Antiviral drugs may be the best candidates for the treatment of Covid-19, until we have specific therapeutic drugs [6]. Oseltamivir (brand name Tamiflu) is a neuraminidase inhibitor approved for the treatment and prophylaxis of influenza A and B ([7,8]).It can inhibit the spread of the influenza virus and reduce viral shedding in respiratory secretions in the human body [8], and is considered a therapeutic option in several clinical trials and studies, but the results remain controversial ([9,10]). More studies are required there to demonstrate the efficacy of antiviral drugs in the treatment of patients with Covid-19.

In this study, our aim was to evaluate the efficacy of Oseltamivir, by comparing two different combination therapeutic regimens, based on length of hospital stay, need for admission to the ICU, mechanical ventilation and mortality rate.

2. Material and methods

2.1. Study design

This was a retrospective analysis of a single center, cohort study, performed between Feb 20, 2020, and April 20, 2020, in patients with Covid-19 infection, at (XXX), a center for pandemic Covid-19 infected patients, (XXX).

This study including 285 confirmed, Covid-19 infected patients who were admitted to this hospital during two months and received two different therapeutic regimens according to the guidelines issued by Iranian Ministry of Health and Medical Education (first edition(11), fifth edition(12).The first group including 120 inpatients between Feb 20, 2020 and March 15, 2020 who received Oseltamivir in addition with routine regimen (combination group) [11].The second group including 165 patients between March 20, 2020 and April 20, 2020 received routine regimen alone (control group) [12].

2.2. Study population

The confirmed Covid-19 infected in patients with mild to severe disease were enrolled in the study, according to their clinical symptoms with a positive diagnostic kit result (RT-PCR) or typical radiologic changes on chest computed tomography (CT) [13], with the approval of the specialist in this hospital for the diagnosis of Covid-19, and clinical requirement of hospitalization(11).

The patient's medical information including demographic data, clinical features, the result of Covid-19 test (PCR), chest CT scans, comorbidities, and underling disease (hypertension, diabetes, pulmonary disease, cardiovascular and kidney disease), the admission to the intensive care unit (ICU), the requirement of mechanical ventilation, the duration of hospitalization, their outcome, and mortality, extracted from hospital documented patient's data recorded in this hospital.

Patients with a history of allergic reactions or known contraindications (QT-prolongation) or drug interactions with routine regimens, or lack of data in their documents, and the patients who die within the first 24 h of hospitalization, exclude from study.

The patients in this study were enrolled by simple random sampling without stratification.

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the (XXX).

Written informed consent was obtained from all patients when admitted to the hospital. patients' confidentiality was considered by protecting their data and documents.

2.3. Intervention and measurement

The routine regimen includes the following: Azithromycin 500 mg/day, Hydroxychloroquine 200 mg/12 h (subgroup A), which can fallow with Lopinavir/ritonavir (200/50 mg tablets two times/12 h) if the patient needs and their hospitalization continued and their conditions worsened, with or without Ribavirin (1200 mg/daily) (subgroup B).

Patients received Acetaminophen for fever as needed, Antiacid (Pantoprazole) for the prevention of stress-induced gastritis or drugs, and other empiric antimicrobial treatments for secondary bacterial pneumonia if necessary (Levofloxacin 500 mg/day, vancomycin 1gr/12 h, meropenem 1gr/8 h, ceftriaxone 1gr/12 h).

The severity of the patient's disease evaluated with the National Early Warning Score (NEWS) which is used to standardize the assessment of the severity of acute illness in the NHS [14], in this scoring we gave scores to vital signs (PR,RR,T,SO2,SYS BP), the level of consciousness and the need for additional oxygen at the first visit when admitted, scores between 1 and 4 show mild disease, 5–6 show moderate disease and$\geq$7 show severe disease, and the degree of involvement of their lungs on chest CT scans to compare the severity of disease between our two groups with an expert radiologist in this hospital, according to this score both lungs divided into 5 lobes and each lobe can get a score of involvement between 1 and 5 so every CT scans scored between 1 and 25 [15].

2.4. Therapeutic effects

In this study we compare a combination of oseltamivir with the routine regimen (oseltamivir group), with the routine regimen alone as a control group (control group), to evaluate the efficacy of oseltamivir in the treatment and outcome of Covid-19 infected patients.

The primary endpoint was the duration of hospitalization (length of hospital stay). Secondary endpoints were the requirement for admission to the intensive care unit (ICU), mechanical ventilation and discharge or mortality of the patient. The patients were followed up for two weeks for therapeutic effects.

2.5. Statistical analysis

Statistical analysis was performed using the STATA version 14. A p value of 0.05 or less ($\leq$0.05) was considered statistically significant. The power of study was 80% and alfa was 0.05.

The descriptive statistic was reported as mean, standard deviation, percentage, and frequency. The confidence interval was 0.95 (Cl, 0.95).

Independent samples the T test and the chi-square test were used to compare the differences between the baseline characteristics of two groups.

Linear regression analysis was used to investigate the relationship between continues outcomes and treatment. Besides, a logistic regression was used to investigate the relationship between binary dependent variables and treatment. Adjustment for severity was performed by multiple linear and multiple logistic regression.

The unique identifying number is: researchregistry7665.

The methods were specified in accordance with STROCSS guidelines [16].

3. Result

3.1. Patients' characteristics

A total of 285 confirmed Covid-19 patients, after initial screening and excluding, were enrolled in the study during two consecutive months of the study period and subdivided into two groups.

The baseline characteristics of all enrolled patients are shown in Table 1. As shown in this table, the patients had no significant differences between the two groups regarding the demographic data, baseline characteristics and underlying diseases.

Patient's comorbidities and underlying diseases, including chronic cardiovascular disease, hypertension, diabetes, chronic pulmonary, and kidney disease.

In general, 117 (41.1%) patients were women and 168 (58.9%) were men, their ages ranged from 16 to 91 years (mean = 53.80, sd = 16.71).

Of these identified cases, 120 patients were classified in group 1 (oseltamivir group), who received oseltamivir plus the routine regimen, while 165 patients were classified in group 2 (control group), who were treated with the routine regimen alone. The flow chart of current study is shown in Fig. 1.

The severity of the disease assessed by NEWS scoring [14] and the findings of chest CT scans on admission day [15], was different between two groups and the oseltamivir group had a higher severity score (5.02 vs 4.2, p = 0.01) (Table 2).

3.2. Therapeutic effects of oseltamivir

However, severity of disease in patients in the oseltamivir group were more than the control group (5.02 vs 4.2, p = 0.01), time to recovery and length of stay in hospital were significantly shorter in patients in oseltamivir group (4.9 vs 6.6 days, P < 0.001).

Similarly, the mortality rate was lower in oseltamivir group (1.7% vs 6.7%, p = 0.06) and after adjusting the disease severity by multivariate regression analysis between two groups had a statistically significant difference (OR = 5.29, 95% cl = 1.11,25.02, p = 0.03).

By univariate and multivariate regression analysis, the comparison of the incidence of ICU admission (6.7%, vs 11.5%, p = 0.1), and the incidence of mechanical ventilation (2.5% vs 4.8%, p = 0.3), showed lower percentage in oseltamivir group but did not differ statistically significant.

A comparison of length of hospital stays between two subgroup A together, and two subgroup B together, showed the similar results, were shorter in oseltamivir group, but the other outcomes did not have a particular result and cannot be evaluated due to the small sample size between subgroups A (Tables 3 and 4). Our multivariate regression analysis results showed that by comparing subgroup A1 with subgroup A2, the length of hospital stay was shorter (AOR = 2.2, 95%Cl = 1.48–2.92, P < 0.001) than by comparing group 1 and group2 (AOR = 1.89,95% Cl = 1.03,2.75, P < 0.001), or subgroup B1 with subgroup B2 (AOR = 1.5,95% Cl = 0.18–2.83, P = 0.02). Therefore, it may show that the efficacy of oseltamivir therapy in mild conditions has a better response in duration of recovery and length of hospital stay.

Table 1
Patient demographic data and characteristic for two groups.

	Group 1 N = 120	Group2 N = 165	Total N = 285	p-value
Age,year Mean(sd)	55.09(15.7)	55.32(17.43)	53.80(16.71)	0.5
Sex,number(%) Male	76(63.3%)	92(55.8%)	168(58.9%)	0.3
Female	44(36.7%)	72(43.6%)	117(41.1%)	
Underlying disease Yes,number(%)	56(46.7%)	74(44.8%)	130(45.6%)	0.4

Table 2
Clinical outcome comparison of study population for two subgroup A.

	Univariate analysis			Multivariate analysis	
	Subgroup A1 N = 55	SubgroupA2 N = 76	P-value	B(95%Cl)	**P-value**
Lohs	3.1(1.52)	4.97(2.49)	<0.001	2.2 (1.48–2.92)	<0.001

CL=Confidence interval, B=Regression coefficient, LOHS = Length of hospital stay.

Table 3
Clinical outcome comparison of study population for both group.

	Univariate analysis			Multivariate analysis	
	Group 1 N = 120	Group 2 N = 165	p-value	AOR/B (95% CL)	p-value
Mechanical Ventilation Yes(%)	3(2.5%)	8(4.8%)	0.3	2.32 (o.59,9.11)	0.2
ICU admission Yes(%)	8(6.7%)	19(11.5%)	0.1	2.32 (0.94,5.73)	0.06
Mortality Yes(%	2(1.7%)	11(6.7%)	0.06	5.29 (1.11,25.02)	0.03
LOHS Day(sd)	4.98 (3.44)	6.62(3.88)	<0.001	1.89 (1.03–2.75)	<0.001
NEWS score Mean(sd)	5.02 (2.78)	4.2(2.96)		−0.81(-1.5,-1.3)	0.01
CT scre Mean(sd)	8.45 (4.76)	7.84(5.74)		−0.06(-1.86,-0.65)	0.3

AOR = Adjusted odds ratio, CL=Confidence interval, ICU=Intensive care unit, SD=Standard deviation B=Regression coefficient, NEWS= National Early Warning Score, CT=Computed tomography, LOHS = Length of hospital stay.

Table 4
Clinical outcom comparison of study population for subgroups B.

	Univariate analysis			**Multivariate analysis**	
	SubgroupB1 N = 65	SubgroupB2 N = 89	P-value	AOR/B(95% CL)	P-value
Mechanical ventilation, N(%)	3(4.6%)	7(7.9%)	0.4	1.86 (0.45–7.57)	0.3
Icu admission Yes(%)	8(12.3)	17(19.1)	0.2	1.87 (0.73–4.77)	0.1
Mortality Yes(%)	1(1.5%)	10(11.2%)	0.04	9.89 (1.19–81.83)	0.03
Lohs	6.56(3.81)	8.03(4.29)	0.03	1.5 (0.18–2.83)	0.02

AOR = Adjusted odds ratio, CL=Confidence interval, ICU=Intensive care unit, B=Regression coefficient, LOHS = Length of hospital stay.

4. Discussion

In such an unprecedent pandemic which affect the global public health and make a crisis in every country around the world, there is an urgent need to assess the efficacy of different repurposed and antiviral drugs for treating the patient infected with Covid-19.

Therefore, in this study we evaluate the efficacy of Oseltamivir as a therapeutic option, for confirmed Covid-19 hospitalized patients with mild to severe disease. Oseltamivir is a repurposed approved antiviral drug recommended by CDC for the prevention and treatment of viral influenza infection [17], and is one of the therapeutic options considered for Covid-19 patients([18,19]).

In a review study in China, revealed that between 96-virus drug and 78 small molecules and after evaluation and computation a complete genomic sequence similarity of virus and chemical structure similarity of

drugs, the predicted top three antiviral drugs against SARS-COV-2 are remdesivir, oseltamivir, and zanamivir, and after molecular coupling showed that these three drugs have higher molecular binding energies with ACE2(9).

Similarly, another study showed that neuraminidase inhibitors improve the survival rate of mice in clinically relevant models of sepsis and regulate the neutrophil response by inhibiting neuraminidase-mediated neutrophil dysfunction (overactivation) in vivo, resulting in infection control and suggest oseltamivir as it could be repurposed for the treatment of sepsis or severe infections such as Covid-19, and raised the requirement for the clinically used neuraminidase inhibitors in sepsis and Covid-19 to explore this hypothesis [20].

In this study, we showed that oseltamivir in combination therapy within the first hours of admission (group 1), was associated with a decreased incidence of ICU admission and mechanical ventilation in compare with control group (group2) which was not statistically significant, and a significant lower mortality rate especially in moderate to severe conditions (subgroup B, $p = 0.04$).

Similar results obtained from a retrospective single center cohort study including 1190 patients with Covid-19 in wuhan, china showed that administration of oseltamivir was associated with a lower rate of mortality in sever patients [21].

In addition there are reassuring safety data for use of oseltamivir in pregnant women that can be prescribe during pregnancy [22].

In some studies the efficacy of oseltamivir treatment for Covid-19 patients remain controversial and further studies requirements for evaluating the efficacy of this drug suggested ([10,23]). However, another study showed that oseltamivir did not have efficacy for the treatment of patients with Covid-19 and was not recommended ([24–26]).

Since Covid-19 infection is a viral disease, and like most drugs for acute infections, an antiviral may be much more potent if given early, says Stanley Perlman, a coronavirus researcher at the University of Iowa, and he said although remdesivir is the best antiviral drug in many studies, but the big challenge is how we could give an expensive intravenous drug like that to people who walk in with mild symptoms and considering that 85% of patients will not develop sever disease and need such a drug like it [5]. Similarly in another study showed that early (within 24 h of fever onset) administration of oseltamivir in combination with antibiotic help a faster improvement in patient's symptoms in Covid-19 suspected outpatients without hypoxia [27].

There for an important consideration in the effective management of Covid-19 as a viral infection is to start an antiviral agent in the first days of infection which is the replication phase of the virus [28].

In our study, we found patients who were treated with oseltamivir in combination therapy within the first hours after admission, showed faster recovery and discharge from the hospital, and had a shorter hospital stay compared to the control group, which was statistically significant ($B = 1.89$, $p < 0.001$) especially under mild conditions (subgroup A, $B = 2.2$, $P < 0.001$).

This may show that the immunomodulatory and probable antiviral effects of hydroxychloroquine ([27–29]) and antibiotic therapy with Azithromycin with triple therapeutic effects (anti-inflammatory, antiviral, antimicrobial) ([29,30]) alone may not be effective in treating Covid-19 disease in the absence of effective antiviral drugs against this viral infection, starting and prescribing as soon as possible. So may be oseltamivir as an oral, nonexpensive antiviaral drug from the repurposed drugs which is already approved for other disease and have acceptable safety profile and a few well-known adverse effects, could consider as a therapeutic option for the initial treatment of Covid-19 patients at the first visit in the office or in the health care centers in combination with an oral antibiotic for prevention of probable secondary bacterial infections and an anti-inflammatory agent. Thus, we could have a faster recovery of disease, and in this way, we could prevent the transmission of the virus from infected patients and progression of the disease in the society for a better control and management of this disease (8).

5. Conclusion

In conclusion, oseltamivir in combination with routine regimen therapy was found to be more efficacious as compared to routine regimen alone, in rapid recovery and earlier discharge of hospital, and was associated with lower mortality rate.

The limitation of our study, is the retrospective nature of this study, incomplete medical records that we had to remove a number of patients, small sample size especially for better results in mortality rate, and the patients were not evaluate at the same time and were reviewed in two consecutive months.

More prospective studies are required to clarify the clinical benefits of oseltamivir in combination therapy and compare oseltamivir with other antiviral drugs for better management and found a well-established gold standard therapy for the treatment of Covid-19 diagnosed.

Ethical approval

All procedures performed in this study that involved human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the Declaration of Helsinki of 1964 and its subsequent amendments or comparable ethical standards.

Sources of funding

No funding was secured for this study.

Author contribution

Abolfazl Zendehdel: conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript, Dr. Saeed Reza Jamali Moghaddam siyahkali and Dr. Azadeh Asoodeh: Designed the data collection instruments, collected data, performed the initial analyzes, and reviewed and revised the manuscript. Dr. Mohammad Bidkhori and Dr. Mohsen Ansari: Coordinated and supervised data collection and critically reviewed the manuscript for important intellectual content.

Registration of research studies

Name of the registry: N/a.

Unique Identifying number or registration ID: IR.TUMS.MEDICINE.REC.1399.396.

Hyperlink to the registration (must be publicly accessible): https://ethics.research.ac.ir/ProposalCertificateEn.php?id=102070&Print=true&NoPrintHeader=true&NoPrintFooter=true&NoPrintPageBorder=true&LetterPrint=true.

Guarantor

Abolfazl Zendehdel.

Consent for publication

Not applicable.

Availability of data and material

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Consent to participate

From the under 16 years old was given by a parent or legal guardian.

Declaration of competing interest

The authors deny any conflict of interest in any way or by any means during the study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2022.103679.

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