Efficacy of Oseltamivir in the Treatment of Patients Infected with Covid-19

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Abstract

Background and purpose: The recent unprecedented pandemic caused by Sars-Cov-2, is threatening public health over 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. Experimental approach: This is a retrospective, according to the date of admission, the patients were divided into two groups; group 1 (oselta group) from Feb 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 including Azithromycin 500 mg/daily and Hydroxychloroquine 200 mg/12h. The endpoints including, the duration of hospitalization, requirement to intensive care unit (ICU) admission and mechanical ventilation, the outcome and rate of mortality. Key Results: A total of 285 patients were enrolled over the two months, 120 patients for group 1 and 165 for group 2. The median time from admission to discharge was significantly shorter in oselta group in comparison with control Group. Additionally, the mortality rate was found to be lower in oselta group than control group which was statistically significant by multivariate analysis. The incidence of ICU admission and mechanical ventilation were also decreased in oselta group but were not found to be statistically significant. Conclusion and implications: 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.

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 specimens of the patient's airway epithelial cells, a novel coronavirus was detected and described as 2019-nCov, and was 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 (Zhu et al., 2020).

This new virus is the seventh human coronavirus described to date as being responsible for respiratory infections (Devaux, Rolain, Colson, & Raoult, 2020), and categorized in the Betacoronaviruse subgroup(Zhu et al., 2020).

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 (Kupferschmidt & Cohen, 2020). So WHO considered a Solidarity and a major study, on March 20, 2020 to collect scientific data and compare therapeutic strategies for defining an effective treatment for patients with Covid-19, wants the hospitals overwhelmed by Covid-19 patients to participate, and from the physicians to simply record their results as the duration of hospital stay, whether the patients required intensive care unit (ICU) admission

or ventilation and the day patient left the hospital or died. "That's all" says Ana Maria Henao Restrepo, a medical officer at WHO's Emergencies Programme (Kupferschmidt & Cohen, 2020).

There for 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 (Kivrak, Ulaş, & Kivrak, 2021). Oseltamivir (brand name Tamiflu) is a neuraminidase inhibitor that is approved for treatment and prophylaxis of influenza A and B ((Yousefi, Mashouri, Okpechi, Alahari, & Alahari, 2021),(Agrawal, Goel, & Gupta, 2020)).It can inhibit the spread of the influenza virus and reduce viral shedding in respiratory secretions in the human body (Agrawal et al., 2020), and is considered as a therapeutic option in several clinical trials and studies but the results remain controversial ((Zhou et al., 2020),(Ungogo, Mohammed, Umar, Bala, & Khalid, 2021)). There for further studies are required to demonstrate the efficacy of antiviral drugs for the treatment of Covid-19 patients.

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

Material and methods

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 Ziaeian Hospital, a center for pandemic Covid-19 infected patients, Tehran, Iran.

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(*Iranian Ministry of health and Medical Education* , 28 Feb 2020), fifth edition(*Iranian Ministry of Health and Medical Education* , 25 march 2020)).The first group including 120 inpatients between Feb 20, 2020 and March 15, 2020 who received Oseltamivir in addition with routine regimen (combination group) (*Iranian Ministry of health and Medical Education* , 28 Feb 2020).The second group including 165 patients between March 20,2020 and April 20,2020 received routine regimen alone (control group) (*Iranian Ministry of Health and Medical Education* , 25 march 2020).

Study population

The confirmed Covid-19 infected inpatients 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 at chest computed tomograph (CT) (Fang et al., 2020), with the approval of the specialist in this hospital for Covid-19 diagnosis, and clinically requirement of hospitalization(*Iranian Ministry of health and Medical Education* , 28 Feb 2020).

The patient's medical informations including demographic data, clinical features, the result of Covid-19 test (PCR), chest CT scans, comorbidities and underling disease (hypertention, diabete, 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 hours of hospitalization, exclude from study.

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 Tehran University of Medical Science (Ethic number : IR.TUMS.MEDICINE.REC.1399.396)

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

Intervention and measurement

The routin regimen include: Azithromycin 500 mg/daily, Hydroycholoroquine 200 mg/12 h (subgroup A), which can fallowed with Lopinavir/ritonavir (200/50 mg tablets two times/12h) if patients need and their hospitalization continued and their conditions worsened, with or with out Ribavirin (1200 mg/daily) (subgroup B).

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

The severity of patient's disease evaluated with National Early Warning Score (NEWS) which is used for standardizing the assessment of acute illness severity in the NHS (physicians, 2017), in this scoring we gave scores to patients vital signs (PR,RR,T,SO2,SYS BP), the level of consciousness and requirement to supplemental oxygen at the first visit when they admitted, scores between 1-4 show Mild disease, 5-6 show Moderate disease and >=7 show severe disease, and the degree of involvement of their lungs at 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 to 5 so every CT scans scored between 1 to 25 (Assistant, 2020).

Outcome

In this study we compare a combination of oseltamivir with routine regimen (oselta group), with 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). The secondary endpoints were, requirement to admission to the intensive care unit (ICU), mechanical ventilation, and patient's outcome discharge or mortality.

Statistical analysis

The statistical analysis was performed using statistical package STATA version 14. A p value of 0.05 or less (<=0.05) was considered statistically significant. The power of study was 80% and alfa was 0.05.

Descriptive statistic was reported as mean, standard deviation, percentage and frequency. Confidence interval was 0.95 (Cl, 0.95).

Independent samples T test and chi-square test was used to compare the differences between 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.

Result

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 study period, and subdivided in two groups (fig 1).

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.

Overall, 117 (41.1%) Patients were female and 168 (58.9%) were male, their ages ranged from 16 to 91 years old (mean=53.80, sd=16.71).

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

The disease severity assessed by NEWS scoring (physicians, 2017) and chest CT scans findings on the admission day (Assistant, 2020), was different between two groups and oselta group had a higher severity score (5.02 vs 4.2, p=0.01) (Table 2).

Therapeutic effects of oseltamivir

However, severity of disease in patients in the oselta 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 oselta group (4.9 vs 6.6 days, P<0.001).

Similarly, the mortality rate was lower in oselta 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 oselta 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 oselta group, but the other outcomes did not have a particular result and cannot be evaluated due to the small sample size between subgroups A (table 3,4). Our results of multivariate regression analysis showed that by comparing subgroup A1 with subgroup A2, length of hospital stay was shorter (AOR=2.2, 95%Cl=1.48-2.92, P<0.001) than 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, maybe it can show that, the efficacy of oseltamivir therapy in mild conditions have a better response in duration of recovery and length of hospital stay.

Discussion

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

Therefor, in this study we evaluate the efficacy of Oseltamivir as a therapeutic option, for confirmed Covid-19 hospitalized patients with mild to sever disease. Oseltamivir is a repurposed approved antiviral drug recommended by CDC for the prevention and treatment of viral influenza infection (Ishaqui et al., 2020), and is one of the therapeutic options considered for Covid-19 patients((Ding, Zhu, & Yao, 2020),(Jiang et al., 2020)).

In one review study in china, revealed that between 96-virus drug and 78 small molecules and after evaluation and compution a complete genomic sequence similarity of virus and chemical structure similarity of drugs, the predicted top three antiviral drugs against SARS-COV-2 are remedesivir, oseltamivir and zanamivir, and after molecular docking showed that these three drugs have higher molecular binding energies with ACE2(Zhou et al., 2020).

Similarly in another study, showed that neuraminidase inhibitors enhances the survival rate of mice in clinically relevant models of sepsis and regulate neutrophil response by inhibition of 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 sever infections such as Covid-19, and it raised the requirement of the clinically used of neuraminidase inhibitors in sepsis and Covid-19 to explore this hypothesis (Formiga et al., 2020).

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 sever 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 (Liu et al., 2020).

In addition there are reassuring safety data for use of oseltamivir in pregnant women that can be prescribe during pregnancy (Louchet et al., 2020).

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 ((Wu et al., 2020),(Ungogo et al., 2021)). Whereas, in another studies showed that oseltamivir did not have efficacy for treatment of Covid-19 patients and was not recommended ((Lam, Lombardi, & Ouanounou, 2020),(Tan et al., 2020),(Sanders, Monogue, Jodlowski, & Cutrell, 2020)).

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 won't develop sever disease and need such a drug like it (Kupferschmidt & Cohen, 2020). Similarly in another study showed that early (within 24 hours 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 (Chiba, 2020).

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 (*Iranian Ministry of health and Medical Education* , deceber 2020).

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

This may show that immunomodulatory and probable antiviral effects of hydroxychloroquine ((Yao et al., 2020),(Gautret et al., 2020),(Guastalegname & Vallone, 2020)), and antibiotic therapy with Azithromycin with triple therapeutic effects (anti inflammatory, antiviral, antimicrobial)((Mosquera et al., 2018),(Kakeya et al., 2014)) alone may not be effective in treatment of Covid-19 disease in the absence of an effective antiviral drugs against this viral infection, to start and prescribed 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(Agrawal et al., 2020).

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.

Further 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 diagnosed Covid-19.

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Conflict of interest : The authors deny any conflict of interest in any terms or by any means during the study.

Ethical approval and consent to participate

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

Consent to participate: from the under 16 years old was given by a parent or legal guardian

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.

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Contributors' Statement Page:

Dr. 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, carried out the initial analyses, 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.

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Table1-patient demographic data and characteristic for two groups

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

Table2-Clinical outcome comparison of study population for two subgroup A

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

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

Table3-Clinical outcome comparison of study population for both group

	Multivariate analysis	Multivariate analysis		Univariate analysis	Univariate analysis	Univariate analysis		
	p-value	AOR/B (95%CL)		p-value	Group 2 N=165	Group 1 N=120		
0.2	0.2	2.32(o.59,9.112)	2.32(o.59,9.110)	0.3 0.1	8(4.8%)	3(2.5%)	3(2.5%)	Me
0.06	0.06	2.32(0.94,5.732)	2.32(0.94,5.730)	0.06	19(11.5%)	8(6.7%)	8(6.7%)	Ve
0.03	0.03	5.29(1.11,25.052)	5.29(1.11,25.022)	0.001	11(6.7%)	2(1.7%)	2(1.7%)	lat
<0.001	<0.001	1.89(1.03-2.75)	1.89(1.03-2.75)		6.62(3.88)	4.98(3.44)	4.98(3.44)	Ye
0.01	0.01	-0.81(-1.5,-1.3)	-0.81(-1.5,-1.3)		4.2(2.96)	5.02(2.78)	5.02(2.78)	IC
0.3	0.3	-0.06(-1.86,-0.65)	-0.06(-1.86,-0.65)		7.84(5.74)	8.45(4.76)	8.45(4.76)	ad
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								Ye
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								tal
								Ye
								LO
								Da
								NE
								sco
								Me
								CT
								scr
								Me

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.

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

AOR=Adjusted odds ratio, CL=Confidence interval, ICU=Intensive care unit, B=Regression coefficient,

LOHS=Length of hospital stay