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Role of Quinolone in Management of (COVID-19) Patients

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Abstract

Background: Since the beginning of the COVID-19 pandemic, researchers have focused on repurposing of existing antibiotics, antivirals and anti-inflammatory drugs to find an effective therapy. Fluoroquinolones are broad spectrum synthetic antimicrobial agents, being chemical derivatives of quinoline, the prodrome of chloroquine.

Objectives: This study to determine if respiratory fluoroquinolones as Levofloxacin have a beneficial as an adjunct treatment in COVID-19 and their impact on COVID-19 morbidity and mortality.

Methods: We conducted a retrospective study on patients ≥ 18 years with acute pneumonic (COVID-19) positive PCR with their radiological findings at Ain Shams university isolation hospitals. We compared between HRCT chest severity score at time of diagnosis of COVID-19 and post COVID-19 by 3 months as follow up HRCT severity Score in two different groups (group of azithromycin and group of levofloxacin), We also conducted a comparison of respiratory morbidity of both groups as result of COVID-19 infection in form ICU admission and needing O_2 therapy.

Results: This study included n=101 patients in each group of two antibiotics, in first group of azithromycin where there was 48 cases were male and 53 cases were female, the second group of quinolone as levofloxacin where there was 43 cases were male and 58 were female, there was also highly significant correlation between two groups according age and its mean and standard deviation p value=0.001. We found highly significant results when we compared between HRCT chest severity score at time of diagnosis of COVID-19 and post COVID-19 by 3 months as follow up HRCT severity score in both groups but there was a highly significant results in group of levofloxacin than the group of azithromycin p value=0.001. We also found that the baseline HRCT severity score at levofloxacin gp was higher than baseline HRCT severity score at azithromycin gp and after treatment there is significant decrease at follow up HRCT severity score between the two groups. We also conducted a comparison of respiratory morbidity of both group as result of COVID-19 infection in form ICU admission and needing O_2 therapy and there was no significant value in both groups in this study results.

Conclusion: Respiratory Fluoroquinolones (Levofloxacin) prove to be beneficial as an adjunct treatment in COVID-19.

Keywords: COVID-19 • Antimicrobial agents • Fluoroquinolones

Introduction

In December 2019, Corona virus disease (COVID-19), caused by Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2), has rapidly spread worldwide, which mainly leads to respiratory tractinfection in the form of fever, cough, dyspnea, fatigue associated with myalgia which represent most common clinical symptoms of the disease [1]. Four stages of COVID-19 have been identified: The first stage is characterized by upper respiratory tract infection; the second by the onset of dyspnea and pneumonia; the third by a worsening clinical scenario dominated by a cytokines storm and the consequent hyper inflammatory state; and the fourth by death or recovery [2]. Viral transmition occurs through direct or indirect contact of mucous membranes (eyes, nose, or mouth) with infectious respiratory droplets. Transmission risks increase with period and proximity with the contacts infected persons [3]. Some

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patients with SARS-CoV-2 infection have mild to moderate COVID-19 disease. Others may have COVID-19 pneumonia, acute respiratory distress syndrome, and multiple-organ failure develop, which can lead to death [4]. The reference standard for diagnosis of (COVID-19) is detection of viral nucleic acid using real time Reverse Transcription Polymerase Chain Reaction test (RT-PCR) applied on respiratory tract specimens [5,6]. On the other hand, chest Computed Tomography (CT) may be extremely helpful for the diagnosis, management and follow-up of COVID-19 due to the high sensitivity of CT 97% [7,8].

Since the beginning of the COVID-19 pandemic, researchers have focused on repurposing of existing antibiotics, antivirals and anti-inflammatory drugs to find an effective therapy. Fluoroquinolones are broad spectrum synthetic antimicrobial agents, being chemical derivatives of quinoline, the prodrome of chloroquine. Interestingly, fluoroquinolones may exert antiviral actions against Vaccinia virus, Papovavirus, CMV, VZV, HSV-1, HSV-2, HCV and HIV. A recent *in silico* study has shown that the fluoroquinolones, ciprofloxacin and moxifloxacin, may inhibit SARS-CoV-2 replication by exhibiting stronger capacity for binding to its main protease than chloroquine and nelfinavir, a protease inhibitor antiretroviral drug [9]. Remarkably, fluoroquinolones have shown multiple immunomodulatory actions leading to an attenuation of the inflammatory response through the inhibition of pro-inflammatory cytokines [10]. Noteworthy, respiratory fluoroquinolones, levofloxacin and moxifloxacin, constitute first line therapeutic agents for the management of severe community-acquired pneumonia. They are characterized by advantageous pharmacokinetic properties; higher concentrations in the lungs; and an excellent safety profile comparable to other antibiotics used to treat respiratory infections, such as macrolides and b-lactams. Based on their potential antiviral activity and immunomodulatory properties, the favorable pharmacokinetics and safety profile, we propose the use of respiratory fluoroquinolones as adjuncts in the treatment of SARS-CoV-2 associated pneumonia [11].

Materials and Methods

Setting and study design

We conducted a retrospective study, It carried out at Ain Shams university isolation hospitals. This study was conducted on patients ≥ 18 years with acute pneumonic (COVID-19) positive PCR with their radiological findings. We compared between chest HRCT severity score at time of diagnosis of COVID-19 by 3 months later in two different groups (group of azithromycin and group of levofloxacin, compared this score in both groups). The exclusion criteria were any patient who less than 18 years and/or adult with other unstable medical issues.

Data collection

Data was collected from all participants and confidentially maintained, All patients received clinical assessment through full history taking including age, gender, other associated conditions (hypertension, diabetes mellitus and others) and clinical suspicion was established according to the global surveillance for COVID-19 by the World Health Organization of COVID-19 and in the absence of an alternative diagnosis that fully explains the clinical presentation. Vital parameters such as respiratory frequency and O_2 saturation were also collected, Classification COVID-19 patients according to disease severity score was evaluated in all cases. In all patients, nasopharyngeal swabs were collected, followed by RT-PCR assay to confirm the diagnosis. Laboratory assessment (Routine blood tests and Arterial Blood Gas (ABG) tests) were performed for all patients and the following parameters were evaluated (C-Reactive Protein (CRP), D-dimer, lymphocyte count, and PaO_2/FiO_2 ratio). All patients were followed during the observation period on their clinical evolution Radiological HRCT of chest severity score.

We compared between HRCT chest severity score at time of diagnosis of COVID-19 and post COVID-19 by 3 months as follow up HRCT severity Score, We also conducted a comparison of respiratory morbidity of both group as result of COVID-19 infection in form ICU admission and needing O_2 therapy.

Statistical analysis

Data were collected, revised, coded and entered to the statistical package for social science (IBM SPSS) version 20. The quantitative data with non-parametric distribution were presented asmean and standard deviation. Also qualitative variables were presented as number and percentages. The comparison between groups regarding qualitative data was done by using *Chi-square* test when the expected count in any cell found less than 5. The comparison between two independent groups with quantitative data and non-parametric distribution was done by using paired t test. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the A p-value<.05 was used as the level of significance.

Results

Study population and descriptive data

The results shows in Table 1.

	Group of Azithromycin	Group of levofloxacin	t	p
Gender N (%)				
Male	48 (47.5)	43 (42.6)	0.5	0.4
Female	53 (52.5)	58 (57.4)		
Age (years)				
Min-Max	19-85	20-79	3.4	0.001*
Mean± SD	38.7 ± 14.03	44.9 ± 11.7		

Table 1. Distribution of Patients regarding as their age and gender.

Paired t test

This Table shows 101 patients in each group of two antibiotics, in first group of azithromycin where there is 48 cases were male and 53 cases were female, the second group of quinolone as levofloxacin where there is 43 cases were male and 58 were female, in this table shows also highly significant correlation between two groups according age and its mean and standard deviation (Table 2).

	Group of azithromycin	Group of levofloxacin	t	p
Baseline				
Min-Max	0-24	Apr-25	5.3	0.001*
Mean ± SD	10.76 ± 7.22	15.68 ± 5.88		
After 3 months				
Min-Max	0-25	0-19	5.8	0.001*
Mean ± SD	9.27 ± 6.82	3.79 ± 6.44		
t	1.9	19.5		
p	0.06	0.001*		

Table 2. Comparison between chest HRCT severity score at time of diagnosis of COVID-19 and post COVID-19 chest HRCT severity score by 3 months in each group separately and comparison of this score in both groups results.

Paired t test

This table shows comparison between chest severity score at time of diagnosis of COVID-19 and post COVID-19 by 3 months as follow up HRCT severity score groups where is highly significant results in both groups but the comparison of this score in between both groups results shows highly significant results in group of levofloxacin than the group of azithromycin (Figures 1 and 2).

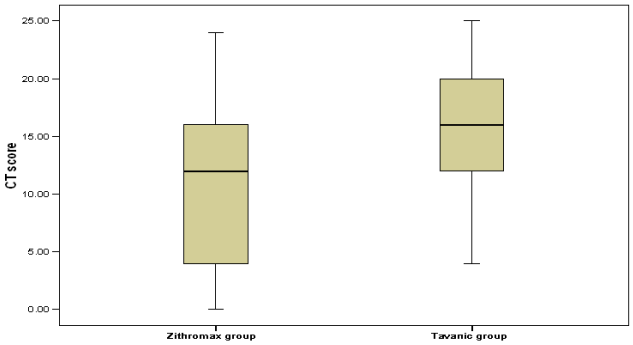

Figure 1. Baseline CT score of both groups

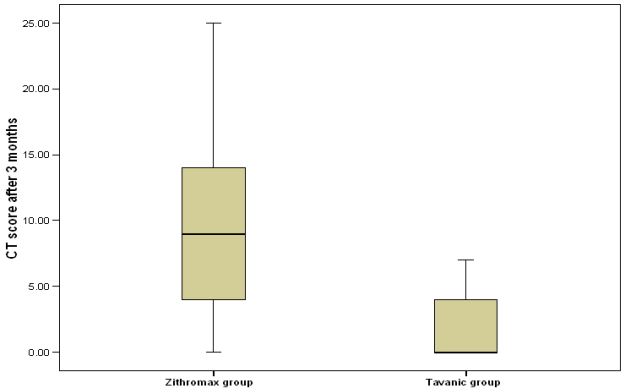

Figure 2. CT score after 3 months of both groups.

The Table 3 shows comparison of respiratory morbidity of both group as result of COVID-19 infection in form ICU admission and needing O_2 therapy where is no significant value in both groups in this study results.

	Group of Azithromycin	Group of levofloxacin	χ^2	p
Need for ICU N (%)				
No	48 (47.5)	35 (34.7)	1.4	0.2
Yes	53 (52.5)	66 (65.3)		
Need for domiciliary O_2 N (%)				
No	53 (52.5)	52 (51.5)	0.02	0.8
Yes	48 (47.5)	49 (48.5)		

Table 3. Comparison between two group of this study regarding the Respiratory Morbidity in form of ICU admission and needing of O_2 therapy.

Discussion

In December 2019, Coronavirus disease (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has rapidly spreadworldwide, which mainly leads to respiratory tractinfection in the form of fever, cough, dyspnea, fatigue associated with myalgia which represent mostcommon clinical symptoms of the disease. Four stages of COVID-19 have been identified: the first stage is characterized by upper respiratory tract infection; the second by the onset of dyspnea and pneumonia; the third by a worsening clinical scenario dominated by a cytokine storm and the consequent hyper inflammatory state; and the fourth by death or recovery. Viral transmition occurs through direct or indirect contact of mucous membranes (eyes, nose, or mouth) with infectious respiratory droplets. Transmission risks increase with period and proximity with the contacts/infected persons. Some patients with SARS-CoV-2 infection have mild to moderate COVID-19 disease. Others may have COVID-19 pneumonia, acute respiratory distress syndrome, and multiple organ failure develop, which can lead to death. The reference standard for diagnosis of (COVID-19) is detection of viral nucleic acid using real time Reverse-Transcription Polymerase Chain Reaction test (RT-PCR) applied on respiratory tract specimens. On the other hand, chest Computed Tomography (CT) may be extremely helpful for the diagnosis, management and follow-up of COVID-19 due to the high sensitivity as described by Ai et al. and Caruso et al. where both studies reported CT sensitivity of 97%. Since the beginning of the COVID-19 pandemic, researchers have focused on repurposing of existing antibiotics, antivirals and anti-inflammatory drugs to find an effective therapy. Fluoroquinolones are broad spectrum synthetic antimicrobial agents, being chemical derivatives of quinoline, the prodrome of chloroquine.

Interestingly, fluoroquinolones may exert antiviral actions against Vaccinia virus, Papovavirus, CMV, VZV, HSV-1, HSV-2, HCV and HIV. A recent *in silico* study has shown that the fluoroquinolones, ciprofloxacin and moxifloxacin, may inhibit SARS-CoV-2 replication by exhibiting stronger capacity for binding to its main protease than chloroquine and nelfinavir, a protease inhibitor antiretroviral drug. Remarkably, fluoroquinolones have shown multiple immunomodulatory actions leading to an attenuation of the inflammatory response through the inhibition of pro-inflammatory cytokines. Noteworthy, respiratory fluoroquinolones, levofloxacin and moxifloxacin, constitute first line therapeutic agents for the management of severe community acquired pneumonia. They are characterized by advantageous pharmacokinetic properties; higher concentrations in the lungs; and an excellent safety profile comparable to other antibiotics used to treat respiratory infections, such as macrolides and b-lactams. Based on their potential antiviral activity and immunomodulatory properties, the favorable pharmacokinetics and safety profile, we propose the use of respiratory fluoroquinolones as adjuncts in the treatment of SARS-CoV-2 associated pneumonia. This study aim to that respiratory fluoroquinolones as levofloxacin, has a beneficial as an adjunct treatment in COVID-19 as the retrospective statistical analysis study of antibiotic use compared with COVID-19 morbidity and mortality. 101 patients in current study where each group of two antibiotics, in first group of azithromycin where there is 48 (47.5%) cases were male and 53 (52.5%) cases were female with mean and SD of age (38.7 ± 14.03) the second group of quinolone as levofloxacin where there is 43 (42.6%) cases were male and 58 (57.4%) were female with mean and SD of age (44.9 ± 11.7), in this study there is a highly significant correlation between two groups according age and its mean and standard deviation was p=(0.001) as levofloxacin mainly use in middle and old age as anti-inflammatory while azithromycin mainly in childhood and young age. Current study shows comparison between chest HRCT Severity Score at time of diagnosis of COVID-19 and post COVID-19 by 3 months as follow up Chest HRCT severity score groups where is highly significant P=(0.001) results in both groups but the comparison of this score in between both groups results shows highly significant results in group of levofloxacin P=(0.001) than the group of azithromycin p=(0.06) [12].

Conclusion

This results was matched with HisayaTanioka; SayakaTaniokaTanioka Clinic, Tokyo, Japan as risks and benefits of antibiotics *vs*. COVID-19 morbidity and mortalitys where the results of study imply that penicillin must be avoided to use under the condition in COVID-19. Empirical treatment with neuraminidase inhibitors and the combination of cephalosporins and macrolides or quinolones are suggested to be an effective treatment for COVID-19. Also they confirmed Macrolides, quinolones, and sulfonates showed a negative correlation tendency with mortality As here was comparison of respiratory morbidity of both group as result of COVID-19 infection in form ICU admission and needing O_2 therapy where is no significant value p=(0.2), P=(0.8) in both groups in this study results. Considering the positive association between antibiotic use and worsening of antibiotic resistance crisis, efforts should be made to strengthen antibiotic stewardship at both national and sub-national levels so as to reduce the long and short impact of antibiotic use in COVID-19 on the antibiotic resistance crisis. Also, data are needed to increase the body of evidence and the clinicians' confidence in the use of antibiotics for COVID-19 diseases.

Conflicts of Interest

None

Availability of Data and Materials

On request, all data will be provided by corresponding author.

Authors' Contributions

All participated in giving the idea of the research and design of the work. MD and DE shared in clinical part of the research at Ain Shams

university hospital. MD, DE and MA contributed to writing, MD contributed to writing (main role). SS was responsible for revision the current research. All authors read and approved the final manuscript.

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