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Original Article

Comparison of Different Treatment Strategies Combating COVID-19 in Pakistan

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ABSTRACT

Objective: To compare different treatment strategies for patients of COVID-19 in Pakistan.
Study Design: Retrospective longitudinal study.
Place and Duration of Study: Abbas Medical Hospital, Muzaffarabad Pakistan, in month of April, 2021.
Methodology: Total of 120, COVID-19 positive patients between 31-45 years of age were admitted at Abbas hospital after carrying out rRT-PCR test. These patients presented with sore throat, cough and fever (>101ºC). These patients were assigned to four different Groups (n=30). Group A was administered Azithromycin while Group B was treated with Azithromycin in combination with hydroxychloroquine. Group C was given combination of oral ivermectin and doxycycline and Group D was treated with lopinavir. Diagnostic tests such as rRT-PCR, blood parameters such as creatinine, random blood sugar, alanine aminotransferase, complete blood count, ECG, chest X-ray and blood biomarkers including procalcitonin, C-reactive protein, lactate dehydrogenase and ferritin were performed at day 1, 5, 7, 14 and 30.
Results: Patients treated with Azithromycin revealed highest recovery of about 93(77.8%+11.68) among COVID-19 patients followed by combination of Azithromycin and hydroxylchloroquinone which was 79(65.56%+10.19), combination of ivermectin and doxycycline was 24(19.63%+8.83) and lopinavir was 11(9.06%+5.26) displayed minimum potency in recovering the COVID-19 positive patients (*p*-value=0.000).
Conclusion: Azithromycin was most effective in helping patients recover from COVID-19 followed by combination of Azithromycin and hydroxychloroquine. Patients recovered after treatment with ivermectin doxycycline were lower followed by those who recovered with lopinavir only.

Keywords: Azithromycin, COVID-19, Chloroquine, Doxycycline, Ivermectin, Lopinavir.

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INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-COV-2); has presented a crucial challenge for scientists and doctors across the world. It is also the sole cause of the outbreak of corona-virus disease 2019 (COVID-19). During the past few decades, the endemic outset of middle-east respiratory syndrome (MERS-CoV) and severe acute respiratory-syndrome (SARS-CoV) has been investigated comprehensively.[1] Corona-viruses are associated to family of viruses referred to as Coronoviridae and its subfamily Coronavirinae.[2] Coronaviruses are RNA enveloped viruses that are distinctly found in humans and wildlife.[3]

Coronaviruses are responsible for causing respiratory illnesses in humans. Therefore, Alpha CoVs such as HCoV-NL63, HCoV-229E and beta CoVs such as HCoV-OC43 and HKU1 may be responsible for causing mild upper respiratory tract diseases. Beta CoVs such as SARS-CoV, MERS-CoV and SARS-CoV-2 are deemed highly pathogenic.[4]

Pneumonia cases of unidentified etiology originating in China gained attention in late 2019. The virus from this unexplained pneumonia was isolated from epithelial cells of human airway and labelled as novel-CoV. This novel-CoV is currently referred to as SARS-CoV-2. Hence, COVID-19 was declared as a public health emergency of international concern by World Health Organization.[5]

Corona-viruses cause symptoms such as loss of taste and smell, cough, fever, fatigue, lung infection, breathing difficulty and COVID pneumonia.[6] These viruses also cause hepatic, neurological, enteric and respiratory illnesses.[7]

Pakistan, like most countries throughout the world, is effectively combatting this disease with its limited resources. The mortality rate of COVID-19 patients is particularly lower in Pakistan. However, mortality rate is escalating due to rise in the number of infections. Moreover, no reliable treatment is currently available for COVID-19. Furthermore, numerous

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clinical trials are currently being carried out for finding out the potential treatment strategies for COVID-19.

The identification of potentially effective treatment strategies for prevention and treatment of COVID-19 patients is an unprecedented issue. Furthermore, an effective treatment of this disease subjected to sound evidence is a critical requirement for the clinicians. This study aims to identify various treatment strategies employed for treatment of COVID-19 in Pakistan and effectiveness of these treatment options in the recovery of patients with COVID-19.

METHODOLOGY

The Retrospective longitudinal study was conducted after the ethical approval from Abbas Institute of Medical Sciences, Muzaffarabad (Ref. No. HDC / IRC / 2019 /04 / 004) to validate the efficacy and safety of several drugs in SARS-CoV-2 positive patients altogether with rapidity of viral clearance. The duration of the study was one month i.e April 1st to 30th in which written and oral consent was obtained from all of the participants of study. This study included a total of 120 patients admitted to Abbas hospital, Muzafarabad. The patients who were tested positive for COVID-19 were included and randomly divided into four different Groups referred to as A, B, C, D (n=30). Group A patients were administered oral Azithromycin while Group B patients were treated with oral Azithromycin in a combination with oral hydroxychloroquine. Moreover, Group C patients were given a combination of oral ivermectin and doxycycline and lastly Group D was given oral lopinavir as shown in Table-I.

The patients included in the study were in an age Group of 31-45 years and were admitted to hospital due to COVID-19. All patients tested positive for SARS-CoV-2 after carrying out real time reverse transcription; PCR; (rRT-PCR). Most of the patients presented with symptoms of sore throat, cough and high grade fever (>101^{o}C).

The patients who were allergic to any drug, those who were suffering from any other disease, lactating or pregnant females, patients who were taking medications for other diseases, participants of a recent clinical trial and anyone who had already used Azithromycin, hydroxychloroquine, ivermectin and lopinavir in the past 30 days, were excluded from study.

A complete history was taken and physical examination of selected patients was performed for each patient. Their vital signs: respiratory rate, temperature, oxygen saturation, pulse rate and blood pressure were monitored on regular basis during the treatment. The presence of SARS-CoV-2 was confirmed by collecting nasopharyngeal swabs and then running rRT-PCR test before admitting the patients in the hospital.

Thus, rRT-PCR test was repeated after 5 days and the patients were followed up after fourteen days until rRT-PCR test was negative. Blood parameters: creatinine, random blood sugar, alanine aminotransferase and complete blood count was performed on days 1, 5, 7, 14 and 30. In addition, ECG, chest x-ray and blood biomarkers including pro-calcitonin, C-reactive protein, lactose dehydrogenase and ferritin were also carried out on each of the aforementioned days. Information regarding previous hospitalization, medication, family history, any sort of co-morbidity and demographic data was also collected.

The Data was analyzed by using Statistical Package for the social sciences (SPSS) version 23.00 and MS Excel 2016 software. Mean±SD was calculated for continuous variable. Frequency and percentage was calculated for categorical variables. Chi square test and t test were used. The *p*-value 0.000 was considered significant.

Table-I: Names of Drugs, Doses used for Each Group and the Mechanism of Action of these Drugs

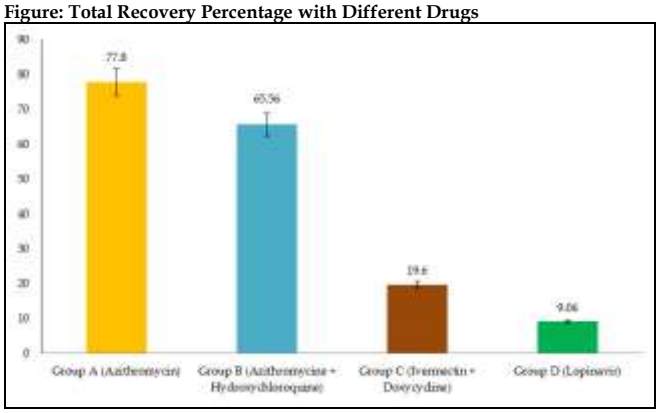
Group	Drugs	Dose	Mechanism of action
A	Azithromycin	Oral 500mg x 1 STAT. Followed by 250mg for 05 days	-Bacterial protein synthesis inhibition. -Antiviral effect.
B	Azithromycin +Hydroxy-Chloroquine	Oral Azithromycin -500 mg x1 STAT; - 250 mg x 4 days -Administered for 5 days. Oral Hydroxychloroquine -400 mg BD x 2 -400 mg OD x 4 days. -Administered for 5 days.	-Bacterial protein synthesis inhibition. -Antiviral effect. -Viral protein synthesis disruption. -Interferes with viral entry and exit through the cell.
C	Ivermectin+ Doxycycline	Oral Ivermectin 12mg x 1 STAT Oral Doxycycline -Doxycycline; 200 mg x 1 dose -Followed by 100mg BD x 3 days for a total of 5 days.	-Antiparasitic drug that halts the replication of viral RNA.
D	Lopinavir	Oral Lopinavir 400 mg BD x 5 days.	-HIV, type 1 protease (HIV-1) inhibitor. -Halts HIV-1. maturation and infectivity; -Same for SARS-CoV-2

RESULTS

The highest percentage of recovery was found in Group A after receiving treatment with Azithromycin

which was 77.8% (SD=11.68, SE=3.41), followed by the recovery in Group B administered with a combination of hydroxychloroquine and Azithromycin was 65.56% (SD=10.19, SE=3.19). The percentage of patients recovered in Group C after treatment with ivermectin and doxycycline was 19.63% (SD=8.83, SE=2.97). The percentage of recovery in in Group D administered with lopinavir was the lowest having value of 9.06% (SD=5.26, SE=2.29) (Figure).

Figure: Total Recovery Percentage with Different Drugs



The patients included in the study were seventy males with mean age Group of 38.24+4.42 years and fifty females with mean age Group of 38.56+4.21 years. The average time duration after which symptoms appeared and patients reported to the hospital was about 4.31+0.052 days and the total stay of patients in hospital was about 30 days. The patients were divided into four Groups; A-D (n=30).

The oral Azithromycin in Group–A relieved symptoms at the highest level for fever which was 27(0.9), sore throat 23(0.77) and cough 20(0.67). The combination of oral Azithromycin and hydroxyl-chloroquine in Group-B had a lower impact on relieving fever 23(0.77), sore throat 22(0.73) and cough 16(0.53). The combination of ivermectin and doxycline in Group–C reduced fever 8(0.27), sore throat 12(0.4) and cough 10(0.33) to a lower extent as compared to Group A and Group B. Oral lopinavir in Group-D had the lowest impact on relieving fever 3(0.1), sore throat 1(0.3) and cough 4(0.13) (*p*-value =0.000) (Table-II).

The proportion% of patients that did not show recovery after utilizing Azithromycin in Group-A for fever was 3(0.1), sore throat was 10(0.33) and cough was 7(0.23) which was calculated to be minimum as compared to other drugs. The patients that did not recover after using combination of Azithromycin and hydroxychloroquine in Group-B for fever was 7(0.23), sore throat was 14(0.23) and cough was 8(0.27). The combination of Ivermectin and doxycycline used in Group-C that did not recover the proportion% of patients in case of fever was 22(0.73), sore throat was 20(0.67) and cough was 18(0.6). The Group-D that contained lopinavir but couldn't recover the proportion% of patients in case of fever was 27(0.9), sore throat was 26(0.87) and cough was 29(0.97). These results were significant at *p*-value =0.000 (Table-II).

Table-II: Comparison of proportion% of recovered and un recovered patients among different drugs and parameters measured

Recovered/ Unrecovered	Drugs				
	Group–A (Azithromycin) Proportion(%) n=30	Group–B (Azithromycin +Hydroxy-Chloroquine) Proportion(%) n=30	Group–C (Ivermectin +Doxycycline) Proportion(%) n=30	Group–D (Lopinavir) Proportion(%) n=30	*p*-value
Fever					
Recovered	27(0.9)	23(0.77)	8(0.27)	3(0.1)	0.000
Unrecovered	3(0.1)	7(0.23)	22(0.73)	27(0.9)	0.000
Sore throat					
Recovered	20(0.67)	16(0.53)	10(0.33)	4(0.13)	0.000
Unrecovered	10(0.33)	14(0.47)	20(0.67)	26(0.87)	0.000
Cough					
Recovered	23(0.77)	22(0.73)	12(0.4)	1(0.03)	0.000
Unrecovered	7(0.23)	8(0.27)	18(0.6)	29(0.97)	0.000

Table-III: Inter Group Proportion Comparison of Different Drug Treatments and Parameters (n=30)

Group Comparisons	Group–A Vs. Group–B	Group–B Vs. Group–C	Group–A Vs. Group–C	Group–B Vs. Group–D	Group–A Vs. Group–D	Group–C Vs. Group–D
Fever	0.13	0.5	0.63	0.67	0.8	0.17
Sore throat	0.14	0.2	0.34	0.4	0.54	0.2
Cough	0.04	0.33	0.37	0.7	0.74	0.37

The proportion difference in the effectiveness of oral Azithromycin in Group–A was maximum and found to be 0.13 with Group-B, 0.63 with Group-C and 0.8 with Group-D in relieving fever. The proportion difference in case of relieving sore throat was 0.14 with Group-B, 0.4 with Group-C and 0.54 with Group-D. The proportion difference in relieving cough was 0.04 with Group–B, 0.37 with Group-C and 0.74 with Group-D. The proportion difference of Group-B and Group-C in relieving fever, sore throat and cough was 0.5, 0.2 and 0.33. The proportion differences in relieving fever, sore throat and cough between Group-B and Group-D was 0.67, 0.4 and 0.7. The proportion difference between Group-C and Group-D in relieving fever, sore throat and cough was 0.17, 0.2 and 0.37. All the values were found to be significant at *p*-value =0.000 (Table-III).

DISCUSSION

After the initial two waves of COVID-19 in 2020, the third wave has emerged recently and is responsible for fatalities among individuals of all age Groups. This has subsequently led to a tremendous burden on the healthcare system throughout the

world. In reference to the COVID-19 cases in each country, a population of 207 million exists in Pakistan where the occurrence and rate of disease transmission has depicted a substantial change amidst third wave of COVID-19. This study provides an insight of various treatment strategies utilized for the treatment of COVID-19 patients at a local healthcare facility in Pakistan and the effectiveness of each of the strategies devised has been documented.

A total of 815,711 confirmed cases presented at several hospitals across Pakistan and a total of 733,062(89.86%) patients recovered after they were provided appropriate treatment. A total of 18,310(2.24%) deaths were reported. According to a report of World Health Organization, Pakistan is currently ranked at 31st place in the world with a total of 827,523 cases and a mortality rate of 0.80 per million (world meter 2021) as of May, 2021.

The current study suggests that about 77.8% of patients in Group-A (n=30) recovered after the treatment with Azithromycin while 65.56% patients in the Group-B recovered after the treatment with a combination of Azithromycin and Hydroxy-Chloroquine. In Group C, 19.63% of the patients recovered after the treatment with a combination of ivermectin and doxycycline, while in the Group D only 9.06% of the patients recovered after they received a treatment with lopinavir (p<0.05) (Figure-I). Thus, the highest number of patients recovered from COVID-19 in the Group A after the administration of Azithromycin (27 patients) followed by the patients in Group B who were given a combination of Azithromycin and hydroxychloroquine (23 patients). On the other hand, the recovery of patients in Group C was lower after the administration of ivermectin and doxycline (8 patients) whereas in the Group D the patients had lowest recorded recovery rate after administration of oral lopinavir (3 patients). Hence, it was concluded that administration of Azithromycin was the most effective treatment regimen in combating COVID-19 as compared to the treatment strategies employed for the other Groups in this study.

Azithromycin is a macrolides and is a commonly known bacteriostatic that is potent enough to interfere with the bacterial growth by inhibiting the bacterial protein synthesis. Furthermore, it exhibits both antibacterial as well as antiviral activities and is utilized for the treatment of viral respiratory tract infections.[8]

Previously, a study performed on the treatment of COVID-19 (Min JY/Korea/2012) concluded that macrolides (Azithromycin) fabricate a potent efficiency against COVID-19 whether used alone or in a combination with other drugs.[8] The recommended oral dose of Azithromycin used for the treatment of COVID-19 is 500 mg STAT on the first day followed by 250 mg, once day for four days making it a total of five days of treatment.[9]

A combination of hydroxychloroquine and chloroquine has been used previously for preventing and treating malaria. In certain cases, this combination has been employed for the treatment of chronic-inflammatory diseases like rheumatoid arthritis and systemic lupus erythematosus. These drugs act by inhibiting glycosylation of host-receptors, proteolytic processing and by, endosomal acidification. These drugs are also responsible for immunomodulatory effects such as inhibition of autophagy of cells, reduction of cytokine-production and by the inhibition of lysosomal activity.[10]

Initial reports proposed that chloroquine was successful for the treatment of COVID-19 patients in China. Patients treated with chloroquine displayed an improved viral clearance and a reduced progression of the disease.[10] The prescribed dose of chloroquine for treating COVID-19 was 500 milligrams once or twice daily through the oral route.[10] Previous literature suggested that optimal dose of hydroxychloroquine in this disease is an initial loading dose of 400 milligrams administered twice daily on the first day followed by a 200 milligram dose of hydroxychloroquine twice daily.[11] This prescribed dose and duration of chloroquine for COVID-19 patients had no adverse effects on the patients. Moreover, the administration of hydroxychloroquine and chloroquine has been considered safe in the patients who were pregnant. There were no documented signs of ocular toxicity in infants born, after the pregnant patients were administered chloroquine or hydroxychloroquine.[12]

Moreover, previous literature suggested that a superior viral clearance was observed in six patients after the administration of hydroxychloroquine supplemented by Azithromycin as compared to those who were exclusively administered hydroxychloroquine.[13] According to a recent study (Bleyzac N/France/2020), the lowest mortality rate was observed in individuals with COVID-19 who were only treated with Azithromycin.[14] The possible reason for this could be that Azithromycin

demonstrates an antiviral activity against few RNA viruses.[15] Moreover, a nonrandomized trial revealed that Azithromycin when combined with hydroxychloroquine demonstrated a considerable antiviral activity against COVID-19.[13]

Ivermectin is a famous and effective antiparasitic drug potent enough to prevent entry of viral proteins into the host cell nucleus thus, acting on the SARS-CoV-2.[16] Recently, a virtual drug screening revealed that doxycycline was potent enough to inhibit the production of papain like proteases in SARS-CoV-2, thus combating the virus.[17]

Previously, in an observational study, the patients displayed a substantial recovery from symptoms of COVID-19 following viral clearance when treated with multiple doses of ivermectin.[18] Furthermore, a retrospective study revealed that ivermectin utilized individually or in combination with other drugs demonstrated a lower mortality rate comparatively.[19] Some of the other studies suggested that a higher concentration of ivermectin exhibited an inhibition of SARS-CoV-2 as compared to the standard dose.[16] However, they have documented side effects such as skin rashes.[20]

Lopinavir/ritonavir is an antiretroviral medication that has also been used for the treatment of patients with COVID-19. A recommended dose of 400 milligrams twice a day for duration of 14 days has been used for the treatment of COVID-19.[21] The patients in such cases need to be monitored continuously and precautions need to be taken before the administration of other medicines when lopinavir or ritonavir is administered. This is due to their potential side effects and drug interactions.

Previously published literature revealed that lopinavir was less effective in reducing death rate or acute respiratory distress syndrome at 21 days as compared to a combination of lopinavir and ribavirin used.[22] The side effects of lopinavir and ritonavir include hepato-toxicity, nausea and diarrhea.[13] The most significantly reported side effects of lopinavir were hepatotoxicity, pancreatitis and cardiac conduction abnormalities.[22]

Previous literature suggests that these side effects may aggravate as a result of viral infection or due to the use of a combination of drugs as certain individuals have higher transaminase levels when they are infected with COVID-19. A recent review of literature suggested that half of the patients that were administered with Ritonavir and lopinavir experienced adverse effects of these drugs and a few of these patients opted for the discontinuation of their treatment due to their gastrointestinal side effects.[21]

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LIMITATION OF STUDY

This study concludes that no potential treatment option is currently available, that can completely cure the patients with COVID-19. Furthermore, a center for disease control and prevention guidance claims that the supportive management of patients with COVID-19 is an appropriate way to deal with its complications and to prevent and control its spread.

CONCLUSION

This study concluded that oral Azithromycin performs an important role in reducing COVID-19 infections as compared to the other treatment strategies. A combination of Azithromycin and hydroxychloroquine was the second most effective treatment regimen. Patients recovered after the treatment with lopinavir, ivermectin and doxycycline were lower as compared to the treatment strategies used in the other Groups in this study.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

AM & MTK: Data acquisition, data analysis, critical review, approval of the final version to be published.

AH & AG: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

EM & AS: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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