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Research Article

A Comparative Study of Hydroxychloroquine and add on Lopinavir-Ritonavir Therapy in Symptomatic COVID-19 Patients-

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ABSTRACT

Purpose: The present study was undertaken to evaluate different management protocols in terms of time duration for seroconversion, hospital stay and severity of COVID-19 infection in COVID-19 patients.

Materials and Methods: An attempt was made to appreciate efficacy and safety of defined management protocol so designed according to molecular pathogenic mechanism of SARS-CoV-2 (Severe Acute Respiratory Syndrome due to Coronavirus 2) in two segregated 104 symptomatic COVID-19 positive admitted patients. Patients managed with Hydroxychloroquine along with standard of care belong to Group 1 while patients treated with combination protocol of Hydroxychloroquine, Lopinavir-Ritonavir along with standard of care put in Group 2. Both management protocols were assessed through variables of time duration for seroconversion, severity of disease process and hospital stay. The antecedent inflammatory parameters of C-Reactive Proteins (CRP), D-dimer, neutrophil/lymphocyte ratio were assayed and comparative evaluation of both management protocols was done.

Results: A total of 104 patients were divided into two respective groups of management protocol with 52 patients in each group. In the study population, most of the patients were young adults with mean age of 45.41 (95% CI 45.41 ± 4.04) year in Group 1 and 50.8 (95% CI 50.8 ± 4.213) years in Group 2. There was a male preponderance with average female to male sex ratio being 0.52 and 0.67 in Group 1 and Group 2, respectively. Mean values of selected inflammatory parameters in serum in Group 1 and Group 2 were observed to be: D-dimer 2.03 µg/mL and 3.01 µg/mL, C-reactive protein 5.2 mg/L and 5.36 mg/L, neutrophil/lymphocyte ratio 2.47 and 2.78 respectively. The mean time duration for seroconversion of COVID-19 patients in Group 1 and Group 2 was 9.92 days and 7.42 days with 95% CI of 3.54 and 1.45, respectively and P-value of less than 0.0001 ($P < 0.0001$). Only 15% patients in the group on HCQ and LPRV took more than 10 days for seroconversion while 34.60% patients in group on HCQ alone took more than 10 days for seroconversion. Mean time of hospital stay for groups 1 and 2 were found to be 10.44 days and 8.59 days respectively. 77% patients got discharged from hospital within 10 days in group treated with HCQ and LPRV as compared to that of 60% in those treated with HCQ alone with P-value of 0.0014 ($p = 0.0014$).

Conclusion: The spectrum of COVID-19 had variable output from different treatment regimens. Patients who were treated with combination regimen of HCQ and LPV/r (group 2) took less time in achieving negative seroconversion and were discharged early from hospital as compared to those treated with HCQ alone (group1).

Keywords: Hydroxychloroquine; Lopinavir-ritonavir; COVID-19; D-dimer

INTRODUCTION

Corona virus 2019 disease (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2), a virus closely related to the SARS virus [1-3]. It was first identified in December 2019 in Wuhan, China, and has since spread globally, resulting in a world-wide ongoing pandemic. As of 15 May 2020, more than 40 lakhs plus cases have been reported across around 200 nations and geographic territories with a mortality of more than 3 lakhs. Corona virus, an enveloped virus belonging to coronaviridae family with a positive-sense extraordinarily large RNA genome has a nucleocapsid of helical symmetry [4] with an incubation period of COVID-19 being five to six days with a range of 2 to 14 days. The most common symptom that COVID-19 positive patients present is fever followed by cough, loss of appetite, fatigue, shortness of breath, sputum production, and muscle and joint pains, nausea, vomiting and diarrhea. Less common symptoms include sneezing, runny nose, or sore throat, decreased sense of smell or disturbances in taste, [5,6] though some COVID-19 positive patients do not develop noticeable symptoms at any point in time. The complications of COVID-19 include pneumonia, Acute Respiratory Distress Syndrome (ARDS), multi-organ failure, septic shock, disseminated intravascular coagulation and death. [7,8] COVID-19 may also present with cardiovascular complications of myocardial infarction, heart failure, arrhythmias, myocarditis and neurologic manifestations of seizure, stroke, encephalitis and Guillain–Barré syndrome [7,8]. Elevated liver enzymes reflecting hepatic injury have also been reported. It has been that SARS-COV-2 has a tropism for ACE2-expressing epithelial cells of respiratory tract. People with COVID-19 and Acute Respiratory Distress Syndrome (ARDS) have classical serum biomarkers of CRS, including elevated C-Reactive Protein (CRP), Lactate Dehydrogenase (LDH), D-dimer, and ferritin [9,10]. The WHO published standard method of testing for COVID-19 is Real-Time Reverse Transcription Polymerase Chain Reaction (RT-PCR) done on respiratory samples obtained by a nasopharyngeal swab [11]. Several existing management protocols are being evaluated for treatment of COVID-19 including chloroquine, hydroxychloroquine, lopinavir/ritonavir and lopinavir/ritonavir combined with interferon beta and remedesvir [12,13].

However, limited therapeutic options are present in terms of efficacy with any single drug regimen [14,15]. Although lopinavir/ritonavir was initially a first line agent in COVID-19 management, a study conducted by Cao, et al. [16] compared lopinavir/ritonavir with standard of care and no benefit was observed in the primary endpoint. It may be pertinent to mention that this study had several limitations. At the same time Chloroquine (CQ) emerged as a potent inhibitor of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS CoV 2) in vitro. CQ and its least toxic derivative Hydroxychloroquine (HCQ), has anti-inflammatory and immunomodulatory effect, wherein it tends to increase endosomal pH and alter glycosylation of angiotensin converting enzyme 2 receptors, thus altering the pathogenesis of COVID-19 in vitro. Thus, combination of HCQ with lopinavir-ritonavir seems to be particularly a plausible definitive management protocol with favorable logistic dynamics.

METHODS

Study design

The present retrospective observational study was conducted on 104 COVID-19 positive patients admitted in S.M.S. Medical College Hospital, Jaipur, Rajasthan from 1st March till 15th May 2020 and symptomatic COVID-19 positive patients were categorized and segregated into two groups with 52 symptomatic patients belonging to each group and clinical comparative evaluation was

done. Asymptomatic patients and critically ill patients were excluded from the study. In group 1, patients received Hydroxychloroquine (HCQ) and WHO specified standard of care for acute respiratory infection and group 2 patients were on Hydroxychloroquine (HCQ) and Lopinavir-Ritonavir (LPV/r) combination therapy with standard of care. The inflammatory parameters like CRP, D-dimer and neutrophil/ lymphocyte ratio were comparatively evaluated in both groups. The duration of COVID-19 RT-PCR conversion from positive to negative, documented as measure of seroconversion and total duration of hospital stay for both groups was comparatively evaluated.

Data collection

The diagnosis of COVID-19 was made based on World Health Organization interim guidance, wherein confirmed cases were positive on RT-PCR assay of nasal and pharyngeal swab specimens [3]. Sample population was segregated and categorized in group 1 and group 2, wherein group 1 sample population were managed with HCQ and standard of care while group 2 were treated with combination therapy of HCQ-LPRV and standard of care. All patients were serially followed up for seroconversion (time duration from positive RT-PCR to first negative RT-PCR for COVID-19) and duration of hospital stay. The severity profile of disease was referenced through laboratory values of inflammatory markers of D-dimer, C-reactive protein and neutrophil/lymphocyte ratio also observed in each group. The data of sample population was compiled and tabulated.

Variables

The patient clinical characteristics were collected at baseline and confirmed cases were diagnosed based on positive viral nucleic acid test result on throat swab samples. The epidemiological variables of age and gender distribution were evaluated. Laboratory markers of inflammation of D-dimer, CRP, neutrophil/lymphocyte ration (N/L ratio) were quantified and used to detect severity of disease in COVID patients. Proportion of patients who recovered from COVID-19 disease were quantified on time scale for their seroconversion time and hospital stay time. Furthermore, the data was used to correlate outcome of the 2 different treatment regimens used in respective categorized groups.

Statistical analysis

The present hospital based, observational descriptive study was carried out on 104 COVID-19 patients at SMS Medical College Hospital, Jaipur in order to investigate epidemiological distribution, laboratory inflammatory parameters, time duration for seroconversion and hospital stay time. The descriptive statistics for quantitative data was expressed as mean and standard deviation and qualitative data was expressed as proportions. The parameters were compared among different groups using chi-square test and z-score for significant differences. The level of significance was assigned at a p-value less than 0.05.

RESULTS

A total of 104 laboratory confirmed COVID-19 patients by RT-PCR admitted at SMS Medical College Hospital, Jaipur, Rajasthan from 1st March to 15thMay 2020, were assessed and serial data from COVID-19 positive patients were collected, evaluated, interpreted and correlated with each other to assess severity of disease and efficacy of two different treatment regimen. These patients were divided into two groups, 52 patients in each group, with different treatment modalities Patients managed with Hydroxychloroquine along with standard of care belong to Group 1 while patients treated with combination protocol of Hydroxychloroquine, Lopinavir-Ritonavir along with standard of care put in Group 2. In the sample population, most patients were young adult in fifth and sixth decade of age and mean age distribution was 45.41 (95% CI: 45.41 ± 4.04) years in Group 1 and 50.8 (95% CI 50.8 ± 4.213) years in Group 2. Difference between mean age of the two group was not statistically significant (p = 0.076) (Table 1,2). In group 1 where all patients treated with HCQ alone, 46.15% patients were < 40 year of age, 35% patients were found to be in age range of 40-60 years while 19.23% patients were above 60 years of age. In group 2 where all patients treated with HCQ and LPRV combination therapy, 28.84% patients were below 40 years of age, 44% patients were in age range of 40-60 years while 26.92% patients were above 60 years of age (Graph 1). There was a male preponderance with average female to male sex ratio being 0.52 and 0.67 in Group 1 and Group 2, respectively. The

Table 1: Epidemiological, Laboratory and treatment output in both in terms of seroconversion and hospital stay groups.

Group 1: Treatment by HCQ alone			**Group 2: Treatment by HCQ+** LPV/r		
Characteristics	**Number of patients**	**Percentage**	**Characteristics**	**Number of patients**	**Percentage**
Age (Mean age = 45.51 year)			**Age (Mean age = 50.8 year)**		
<40 year	24	46.15%	20-40 year	15	28.84%
40-60 year	18	35%	40-60 year	23	44%
>60 year	10	19.23%	>60 year	14	26.92%
Gender (Sex ratio = 0.52)			**Gender (Sex ratio = 0.67)**		
Female	18	35%	Female	21	40%
Male	34	65.38%	Male	31	59.61%
Laboratory parameters			**Laboratory parameters**		
D-Dimer (Mean value = 2.03 µg/mL)			**D-Dimer (Mean value = 3.01 µg/mL)**		
0-0.5	5	10%	0-0.5	6	12%
0.5-2.0	24	46.15%	0.5-2.0	18	34.61%
>2.0	23	44%	>2.0	28	54%
CRP (Mean value = 5.2 mg/L)			**CRP (Mean value = 5.36 mg/L)**		
<3 mg/L	17	33%	<3 mg/L	22	42%
>3 mg/L	35	67.30%	>3 mg/L	30	57.69%
N/L ratio (Mean = 2.47)			**N/L ratio (Mean = 2.78)**		
1.1-3.0	39	75%	1.1-3.0	37	71%
>3.0	13	25.00%	>3.0	15	28.84%
Time for seroconversion (Mean = 9.92 days)			**Time for seroconversion (Mean = 7.42 days)**		
5-10 days	34	65%	<5 days	14	27%
10-15 days	16	30.76%	5-10 days	30	57.69%
>15 days	2	4%	>10 days	8	15%
Time for hospital stay (Mean = 10.44 Days)			**Time for hospital stay (Mean = 8.59 Days)**		
5-10 days	31	60%	<5 days	7	13%
10-15 days	18	34.61%	5-10 days	33	63.46%
>15 days	3	6%	>10 days	12	23%

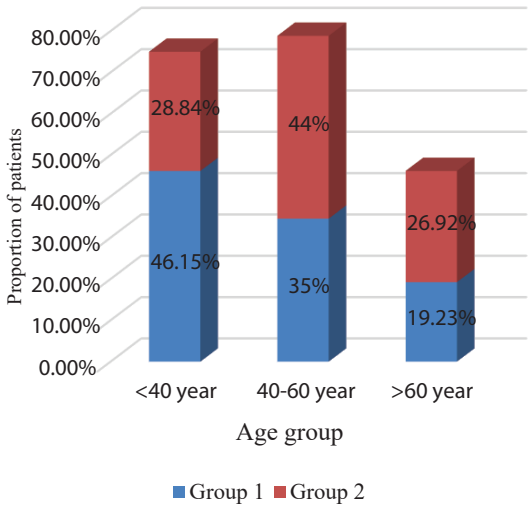
Abbreviations: HCQ: Hydroxychloroquine; LPV/r: Lopinavir-ritonavir combination therapy; CRP: C-Reactive Protein; N/L: neutrophil/lymphocyte ratio.

Table 2: Statistical analysis of study data in both group of patients.

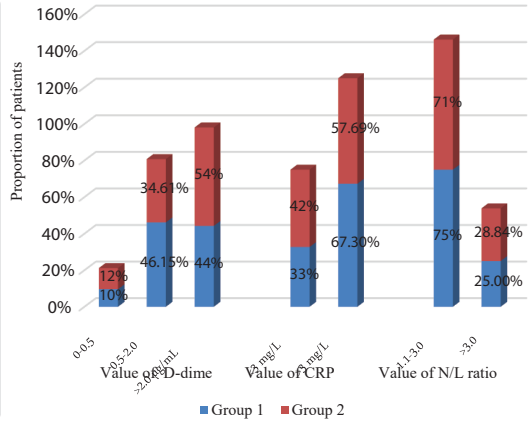
S. No.	Characteristics	Group 1			Group 2			P-value
		Mean value	95% Confidence Interval	standard deviation (SD)	Mean value	95% Confidence Interval	standard deviation (SD)	
1	Age	45.51 year	45.51 ± 4.04	14.8	50.8 year	50.85 ± 4.213	15.34	0.076
2	D-dimer	2.03 µg/mL	2.03 ± 0.36	1.034	3.01 µg/mL	3.01 ± 0.68	2.5	0.0103
3	CRP	5.2 mg/L	5.24 ± 0.91	3.38	5.36 mg/L	5.36 ± 1.21	4.47	0.8304
4	N/L ratio	2.47	2.47 ± 0.32	1.18	2.78	2.78 ± 0.454	1.67	0.2712
5	Duration for seroconversion	9.92 days	9.92 ± 0.70	2.6	7.42 days	7.42 ± 0.81	2.78	<0.0001
6	Duration for hospital stay	10.44 days	10.41 ± 0.71	2.61	8.59 days	8.59 ± 0.88	3.1	0.0014

P values indicate differences between group 1 and group 2 patients. $P < .05$ was considered statistically significant; CRP: C-Reactive Protein; N/L: Neutrophil/ Lymphocyte ratio.

status of Inflammation in each group was profiled through estimation of D-dimer, CRP and N/L ratio. Mean values of D-dimer were observed to be 2.03 µg/mL (95% CI 2.03 ± 0.36) and 3.01 µg/mL (95% CI 3.01 ± 0.68) for group 1 and group 2, respectively with difference across both groups being statistically significant ($p = 0.0103$) (Table 1,2). In group 1 of study population, 10% patients had normal range of D-dimer (<0.5 µg/mL), 46.15% patients had raised D-dimer up to four times of upper limits of normal (ULN) (0.5-2.0 µg/mL) and 44% patients had extremely high value of D-dimer more than four times of ULN (>2.0 µg/mL). In group 2 of study population, 12% patients had normal range of D-dimer (<0.5 µg/mL), 34.61% patients had raised D-dimer up to four times of ULN (0.5-2.0 µg/mL) and 54% patients had extremely high value of D-dimer more than four times of ULN (>2.0 µg/mL). The mean values of CRP for groups 1 and 2 sample population were 5.2 mg/L (95% CI 5.24 ± 0.91) and 5.36 mg/L (95% CI 5.36 ± 1.217), respectively, the difference not being statistically significant ($p = 0.83$). In group 1, 33% patients had normal CRP (<3 mg/L) and 67.30% patients had raised CRP (>3 mg/L) while in group 2, 42% patients had normal CRP (<3 mg/L) and 57.69% patients had raised CRP (>3 mg/L). Mean values of N/L ratio were found to be 2.47 mg/L (95% CI 2.47 ± 0.32) and 2.78 mg/L (95% CI 2.78 ± 0.454) for group 1 and group 2 respectively and the difference between the two groups was statistically not significant ($P = 0.27$). In group 1, 75% patients had normal N/L ratio (1.1-3.0) and 25% patients had raised N/L ratio (>3.0) while in group 2, 71% patients had normal N/L ratio (1.1-3.0) and 29% patients had raised N/L ratio (>3.0) (Graph 2). None of patients had reduced N/L ratio. The mean time duration needed for seroconversion of COVID-19 patients in Group 1 and Group 2 was observed to be 9.92 days (95% CI 9.92 ± 0.70) and 7.42 days (95% CI 7.42 ± 0.81), respectively, the difference being statistically significant (P <0.0001). Seroconversion time duration in group 1 was found to be 5-10 days in 65% patients, 10-15 days in 30.76% and more than 15 days in only 4% patients. Seroconversion time duration in group 2 was found to be <5 days in 27% patients, 5-10 days in 57.69% and more than10 days in only 15% patients. Mean duration of hospital stay for sample patient population belonging to groups 1 and 2 was 10.44 days (95% CI: 10.44 ± 0.71) and 8.59 days (95% CI: 8.59 ± 0.88), the difference in duration of hospital stay between two group being statistically significant ($p = 0.0014$). The hospital stay duration in group 1 was found to be 5-10 days in 60% patients, 10-15 days in 34.61% and more than 15 days in only 6% patients while in group 2, 13% had hospital stay of less than 5 days, majority 63.46% had a stay between 5 to10 days and only 23% patients had a hospital stay of more than 10 days. The proportionate recovery duration and hospital stay were found to be high in patients treated with HCQ alone while it was low in patients treated with combination therapy of HCQ and LPV/r. Inflammatory markers were observed as statistically insignificant in both group except D-dimer which was coincidently observed statistically high in group 2 patients who treated with HCQ and LPV/r combination therapy.



Graph 1: Age distribution of COVID patients in both group.



Graph 2: D-dimer, CRP, N/L ratio in COVID patients in both group.

DISCUSSION

It has been documented, while assessing early transmission dynamics of the virus, that median age of patients afflicted with

COVID-19 is 59 years, with an age range of 15 to 89 years and majority (59%) patients affected are males. It has been suggested that population most at risk may be people with poor immune function such as ageing population and those with preexisting renal and hepatic dysfunction [17]. The severity of COVID-19 positive patients has been profiled as per clinical manifestations, comorbid status, oxygen saturation, requirement of non-invasive or invasive ventilation. In the absence of a definitive treatment regimen, the management protocol of COVID-19 positive patients is presently decided by clinical status of patients, laboratory parameters (inclusive of status of formed and non-formed elements in blood namely cell counts in blood and markers of inflammation), the need for assisted ventilation and other relevant clinical data. Consequently, two different treatment regimens addressing the proposed pathogenetic mechanism was designed with the aim to decrease the viral load and hospital stay. A total of 104 patients were analyzed during the course of the study. Most of COVID-19 patients were in their fifth and sixth decades of life with mean age of patients was 45.4 year and 50 year in group 1 and group 2 respectively. It was further observed that percent of male gender afflicted with COVID-19 was more as compared to that observed for females, though the difference in the selected epidemiological parameters of two groups not statistically significant. The status of inflammation in each group was determined by levels of D-dimer, CRP and N/L ratio in blood. In the present study majority of patients had raised values of D-dimer in both group while blood level of D-dimer was extremely elevated in nearly half of patients in both group (44% in group 1 and 54% in group 2). The mean value of D-dimer was significantly high (3.01 µg/mL) in patients who were treated with combination therapy of HCQ and LPV/r while it was low (2.03 µg/mL) in patients treated with HCQ alone ($P = 0.0103$). The other inflammatory parameters like CRP and N/L ratio was also observed to be elevated in group 2 as compared to that observed in group 1, but the levels were not statistically significant. Blood level of CRP were raised in nearly two third patients (67.30%) of group 1 while it was raised in (57.69%) in group 2. Neutrophil to Lymphocyte ratio was observed to be raised in nearly one fourth patients in both groups suggestive of relative lymphopenia that presumably is secondary to inflammatory cascade in COVID-19 patients, replicative of a viral infection. Relative lymphopenia or high N/L ratio has been found to be slightly high in patients selected for treatment by combination therapy of HCQ and LPV/r but not statistically significant. The duration of seroconversion is another important prognostic tool in treatment of COVID-19 positive patients and it was observed that seroconversion occurred earlier in patients who were treated with combination therapy of HCQ and LPV/r while seroconversion occurred late in patients treated with HCQ alone and difference in duration of seroconversion between the two groups was statistically significant ($p < 0.0001$). Nearly two thirds of patients (65%) of group 1 recovered virologically within 10 days while a higher number of patients (85%) in group 2 recovered in same time duration. The dynamics of time duration of hospital stay mimicked the time curve of seroconversion, subsequently patients on combination therapy of HCQ and LPRV were discharged earlier as compared to patients on HCQ and the difference between two groups was statistically significant ($p = 0.0014$). On conclusion, it was observed that output spectra of COVID-19 is varied dependent on management protocol. Patients who were put on combination regimen of HCQ and LPV/r (group 2) took less time for seroconversion in becoming negative on RT-PCR for COVID-19 and were subsequently discharged earlier from hospital as compared to the group that was treated with HCQ alone (group1). Although coincidently severity of disease in terms of raised D-dimer, CRP, neutrophil/lymphocyte ratio was observed to be higher in group 2.

LIMITATIONS

First, the sample size is small and study is done on hospital based admitted patients. Study of a larger cohort is required to obtain definitive results. Second, there was no definite criteria for selection of patients for different treatment regimen. Value of inflammatory parameters may serve as selection criteria for case control study in future. Third, the susceptibility of COVID-19 was considered (initially and incorrectly) to be very low among infants, children and adolescents, so such sample population was not included in the study. Fourth critically ill patients were not included in our study group.

AUTHOR CONTRIBUTIONS

S. Bhandari, A. Singh and G. Rankawat formulated the research questions, designed the study, developed the preliminary search strategy, and drafted the manuscript; R. Chejara, G. Rankawat, refined the search strategy by conducting interactive database queries and incorporating new search terms; G. Rankawat, A. Singh and R. Chejara collected and analyzed data; S. Bhandari and A. Singh conducted the quality assessment. All authors critically reviewed the manuscript for relevant intellectual content. All authors have read and approved the final version of the manuscript.

Availability of data and materials

Available from corresponding author upon reasonable request.

Declaration of competing interest

All authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential.

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