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Systematic Review

Comparative outcome analysis of hydroxychloroquine/chloroquine, remdesivir and standard of care treatment against COVID-19 infection

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ABSTRACT

This study aimed to compare the efficacy and safety of hydroxychloroquine/chloroquine (HCQ/CQ), remdesivir and standard of care treatment (SOC) in patients with nCoV-19 based on the RCTs available in the literature. We conducted a cumulative review of all the RCTs published for the treatment of nCoV-19. Analysis for odds of patient recovery on HCQ/CQ, remdesivir and SOC treatment was accomplished and recovery was expressed as undetectable viral RNA levels. Total sample size in our analysis was 978 from six RCTs, in which nCoV-19 positive patients treated with HCQ/CQ, remdesivir and SOC were 166, 560 and 252, respectively. SOC treatment showed increase in 2-fold of patients' recovery as compared to the HCQ/CQ group ($p=0.0006$). Further, patients reported 1.5-3-fold increase in adverse events in remdesivir and HCQ/CQ group as compared to SOC group ($p=0.0016$ and $p<0.0001$). Our finding suggests remdesivir or HCQ/CQ ensures no benefit over SOC treatment, which may be attributed to the adverse events exhibited by remdesivir, or inefficacy of HCQ/CQ.

Keywords: nCoV-19, COVID-19, Hydroxychloroquine/chloroquine, Remdesivir, Standard of care

INTRODUCTION

The world health organization has declared novel coronavirus-19 (nCoV-19), outbreak as a global pandemic.¹ As of June 20 2020, nCoV-19 has affected over 8.5 million people worldwide.²

nCoV-19 is a single-stranded RNA-enveloped virus, which binds with host cell surface angiotensin-converting enzyme 2 receptor (ACE2), through its structural spike protein. Entry of virus is facilitated by receptor-mediated endocytosis and the virus releases its RNA into the host cell. Further, the viral RNA is translated into polyproteins for viral replication, and thereby leading to infection of the host cell.³

The virus is isolated from naso and oropharyngeal specimens from putative COVID-19 patients and detected

by reverse transcription polymerase chain reaction (RT-PCR). It is unclear how long patients remain contagious, as a period of infectivity of patients' do not corroborate with viral RNA shedding after resolution of symptoms. The median duration of viral RNA shedding was found to be a minimum of 24 days to a maximum of 42 days.⁴

The spectrum of clinical manifestation is unclear. Symptoms range from mild to moderate and moderate to severe, even leading to death. Common manifestations include sore throat, cough, fever, running nose, myalgia, shortness of breath, pneumonia and multi-organ failure. Severely ill patients suffer from acute respiratory distress syndrome leading to respiratory failure due to alveolar damage. It is commonly observed that elderly and middle-aged patients with comorbidities like coronary heart disease, diabetes, hypertension and renal disease are at more risk to death.⁵

The current recommendations have advocated the use of HCQ/CQ and remdesivir as potential pharmacological agents against nCoV-19. HCQ/CQ is approved for the prevention and treatment of malaria, rheumatoid arthritis, systemic lupus erythematosus and other chronic inflammatory diseases. Antiviral activities of HCQ/CQ seem to prevent viral entry into cells by inhibiting glycosylation of host receptors, proteolytic processing, and endosomal acidification. Immunomodulatory effects occur via decrease in cytokine production, inhibition of autophagy and lysosomal activity in host cells.³ Currently, HCQ/CQ is administered at variable doses (200-800 mg), however, optimal dose to ensure safety and efficacy is debatable. RCTs need to be conducted to explore the optimal dose for nCoV-19 treatment, as we have vast experience in patients with SLE and malaria. The safety issues with HCQ/CQ reported are QTc prolongation, neuropsychiatric effects, hypoglycaemia and retinopathy.³ Therefore, it is recommended to evaluate baseline electrocardiogram before initiating the therapy. Remdesivir is a prodrug that undergoes metabolism to become an active c-adenosine nucleoside triphosphate analogue. It acts by inhibiting RNA dependent RNA polymerase enzyme. Remdesivir has shown antiviral activity against RNA viruses, *Coronaviridae*, *Flaviviridae* and Ebola virus. The current recommended loading dose is 200 mg, followed by 100 mg daily infusion. Multiple-dose administrations can lead to reversible elevation of aspartate aminotransferase and alanine transaminase. It is not recommended in pregnant and lactating mothers, children below 12 years of age and in patients with an estimated glomerular filtration rate less than 30 mL/min.³

Currently, there is neither an established standard treatment guideline nor approval of specific drugs from the United States food and drug administration (U.S. FDA) for the management of nCoV-19 disease. Repurposed drugs with antiviral activity are currently used for the management of nCoV-19. There is an urgent need for specific medication against the current pandemic due to nCoV-19. Further, the data obtained from several observational studies on COVID-19 have been inconclusive. Moreover, limited data is available from randomized clinical trials (RCTs), though multiple RCTs are being conducted for exploring the effective therapeutic strategies against nCoV-19 infection. The safety and efficacy of currently used medications are a matter of debate. Our analysis aimed to compare the superior efficacy of different treatments like HCQ/CQ vs remdesivir vs SOC against nCoV-19 infection, based on the collective data obtained from RCTs.⁶⁻¹¹

METHODS

We reviewed the existing literature on June 20, 2020 for all the RCTs demonstrating the treatment strategies against nCoV-19. The search terms used were (COVID-19 or 2019-nCoV or SARS-CoV-2) and remdesivir and (clinical trial or randomized controlled trial) and (COVID-19) and (randomized controlled trial) in PubMed. We only selected

RCTs to ensure the highest level of evidence for the nCoV-19 treatment.⁴ SOC treatment included, as necessary oxygen supplementation, ventilation support, antibiotic, vasopressor support, renal replacement therapy and extracorporeal membrane oxygenation.⁷ We collected the data from RCTs which comprised of demographic, associated comorbidities, mean duration of treatment, mortality, patient recovered and adverse events. Analysis was performed for odds of patients' recovery on HCQ/CQ vs remdesivir vs SOC treatment and was expressed as undetectable viral RNA levels.

Statistical analysis

Cumulative data from selected RCTs (n=6) were categorized into HCQ/CQ, remdesivir and SOC groups. Baseline demographic characteristics were expressed in mean, ratio and percentages. Odds ratio of recovery in HCQ/CQ, remdesivir and SOC groups was evaluated by Z test with 95% confidence interval (CI) and was represented as forest plot. A Kaplan-Meier plot was used to estimate the overall recovery curves. Recovery curves of the three treatment groups were compared using the log-rank test.

RESULTS

The total sample size in our analysis was 978 from six RCTs, in which 166 COVID-19 positive patients received HCQ/CQ, 560 subjects were treated with remdesivir and 252 patients received SOC treatment. Mean age of the study subjects was 47, 64 and 55 years, respectively. The number of male patients were 110 in HCQ/CQ, 342 in remdesivir and 150 in SOC group. The severity of the patients was categorized as a ratio of mild to moderate and severe, which was 78:88, 0:560 and 75:178, respectively. In each group, comorbid conditions i.e. diabetes and hypertension were recorded. 16% of patients were diabetic in HCQ/CQ group, while 23 and 15% of subjects were found to be diabetic in remdesivir and SOC group, respectively. Hypertension was observed in 19% of patients on HCQ/CQ as compared with up to 48 and 13% of subjects in remdesivir and SOC-treated group. Mean duration of treatment was 11, 8 and 10 days in each group. At the end of the study, the mortality rate was observed in HCQ/CQ group was 13 and 11% in remdesivir group and 14% in SOC group. The patients' survival rate at the end of the study period was 42, 89 and 85% in all the respective groups (Table 1). Probability of negative conversion, which was expressed as undetectable viral RNA count was higher as 62% in SOC group as compared to 45% in HCQ/CQ group and 58% in remdesivir group (OR=2.0052, p=0.0006 and OR=0.8368, p=0.2525) (Table 1 and 2). In HCQ/CQ group, 56% patients experienced adverse events, 69% in remdesivir group as compared to 42% in SOC group (OR=1.7707, p=0.0016 and OR=3.1071, p<0.0001) (Table 1 and 3). The overall patients' recovery was 45% in HCQ/CQ group, while 58 and 62% observed in remdesivir and SOC group, respectively (p=0.0036, p=0.0006) (Figure 1 and 2).

Table 1: Comparative analysis between hydroxychloroquine/chloroquine, remdesivir and standard of care.

Characteristics	HCQ/CQ ^{6,8,11}	Remdesivir ^{9,10}	SOC ⁷⁻⁹
Sample size (n)	166	560	252
Mean age (years)	47	64	55
Gender (M:F)	110:56	342:218	150:102
Severity (mild to moderate:severe)	78:88	0:560	75:178
Co-morbidities			
Diabetes (%)	27 (16)	130 (23)	38 (15)
Hypertension (%)	32 (19)	270 (48)	33 (13)
Mean duration of treatment (days)	11	8	10
Doses (mg)/route	450,600,800/oral	100/IV	-
Mortality (%)	22 (13)	59 (11)	35 (14)
Patient's survived (%)	69 (42)	501 (89)	213 (85)
No. of patients recovered (%)	75 (45)	325 (58)	157 (62)
Adverse events (%)	93 (56)	388 (69)	106 (42)

HCQ/CQ-hydroxychloroquine/chloroquine, SOC-standard of care

Table 2: Odds ratio for patients' recovery, depicting the comparison in treatment efficacy among HCQ/CQ, remdesivir and SOC groups.

Groups	Odds ratio	95% CI	Z-test	P value
SOC vs remdesivir	0.8368	0.6168 - 1.1354	1.144	0.2525
SOC vs HCQ/CQ	2.0052	1.3469 - 2.9852	3.427	0.0006*
Remdesivir vs HCQ/CQ	0.5959	0.4205 - 0.8446	2.909	0.0036*
SOC vs other treatments	0.7424	0.5535 - 0.9960	1.987	0.0469*

HCQ/CQ-hydroxychloroquine/chloroquine, SOC-standard of care, other treatments-cumulative data from remdesivir and HCQ/CQ grp.

Table 3: Odds ratio for patients' adverse safety events, illustrate the comparisons among HCQ/CQ, remdesivir and SOC groups

Groups	Odds ratio	95% C. I	Z test	P value
Remdesivir vs SOC	3.1071	2.2837-4.2273	7.217	<0.0001*
HCQ/CQ vs SOC	1.7547	1.1814-2.6062	2.786	0.0053*
Remdesivir vs HCQ/CQ	1.7707	1.2413-2.5258	3.153	0.0016*
SOC vs other treatments	0.3698	0.2757-0.4960	6.640	<0.0001*

*P value <0.05 was considered significant.

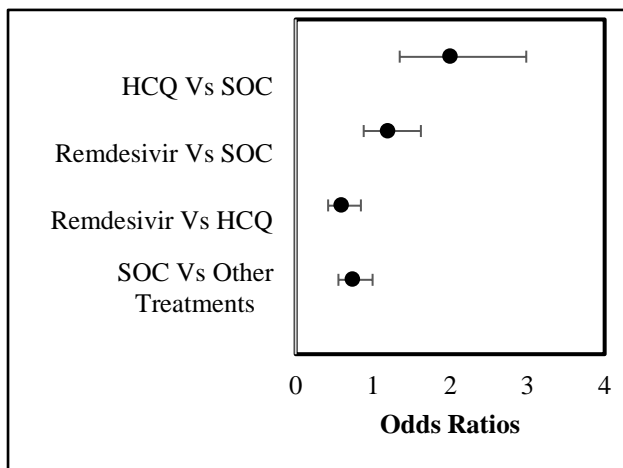


Figure 1: Forest plot of odds ratio for patients' recovery, depicting comparison in treatment efficacy among HCQ/CQ, remdesivir and SOC groups.

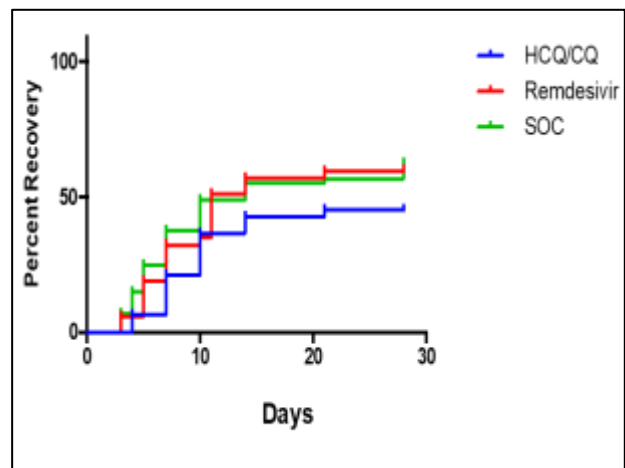


Figure 2: Comparison of cumulative patients' recovery rate between HCQ/CQ, remdesivir and SOC groups. P values (log rank test) was 0.0006.

DISCUSSION

Based on the existing literature on RCTs, our study compared the efficacy and safety of HCQ/CQ, remdesivir and SOC treatment. The virologic clearance was considered as a gold standard indicator for patients' recovery, which was used as an efficacy parameter in all the previous RCT studies. Adverse events were also monitored during the follow-up period as a safety outcome measure.

Some studies have shown the beneficial effect of HCQ/CQ and remdesivir for the treatment against nCoV-19 patients. Gao et al reported the efficacy and safety of chloroquine against COVID-19 associated pneumonia from multi center clinical trials. They demonstrated improved outcomes in terms of radiologic findings, enhanced viral clearance, and reduced disease progression.¹² However, the use of chloroquine is associated with more chances of adverse drug reactions. Another study by Gautret et al, was an open-label nonrandomized clinical study, enrolled 36 patients with a follow-up of 6 days (20 in the HCQ group with a dose of 200 mg orally every 8 hourly and 16 in the control group receiving standard supportive care). At the end of the study, improved virologic clearance was seen in HCQ group as compared to control group ($p=0.001$).¹³ Limitations of the study were a small sample size, non-random allocation of participants and small duration of follow-up. Jacobs et al reported the first clinical use of remdesivir for the treatment of Ebola.¹⁴ Holshue and Kujawski et al reported successful use of remdesivir for COVID-19.^{15,16} However, efficacy of remdesivir cannot be ascertained on the basis of case reports.

Our results demonstrated that neither HCQ/CQ nor remdesivir showed superiority in efficacy and safety in comparison to standard of care treatment. As there are limited evidence from available RCTs, our analysis showed that the odds of recovery in nCoV-19 positive patients were observed to be highly significant with SOC in comparison to HCQ/CQ-treated group. However, the efficacy of remdesivir was comparable to SOC, though, safety issues with remdesivir and HCQ/CQ are still a matter of concern. HCQ/CQ used alone or in combination poses chances of additive cardiotoxicity and evidence for appropriate effective dose is lacking that does not support adoption of any regimen without additional RCTs.³ The clinical trial demonstrated the safety and pharmacokinetics parameters in single and multiple-dose of remdesivir. Intravenous infusions between 3 mg and 225 mg were well-tolerated without any evidence of liver or kidney toxicity. However, previous observational studies demonstrated limitations of its use in patients with deranged liver and renal functions.³ Therefore, we advocate the use of large scale of RCTs to establish a better alternative treatment strategy with profound efficacy and safety to curtail the prevailing nCoV-19 pandemic. To the best of our knowledge, this is the first cumulative analysis of the published RCTs to elucidate the safety and efficacy of currently used medication for nCoV-19.

CONCLUSION

We conclude based on our findings that remdesivir or HCQ/CQ exerts no beneficial effect over SOC treatment, which may be due to the inefficacy of curative potential of HCQ/CQ, and the occurrence of adverse drug events by remdesivir treatment.

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