ECRONICON OPEN ACCESS

EC PULMONOLOGY AND RESPIRATORY MEDICINE

Research Article

Is Hydroxychloroquine "The Silver Bullet"? Role in Healthcare Workers as a Prophylactic Agent against Covid-19

Desh Deepak[1]*, Gowtham Reddy[2§], Amit Suri[3§], Kushagar Garg[4§] and Minakshi Bhardwaj[5]

[1]Senior Respiratory Physician, Department of Respiratory Medicine, Dr Ram Manohar Lohia Hospital and Atal Bihari Vajpayee Institute of Medical Sciences, New Delhi, India

[2]Resident, Department of Medicine, Dr Ram Manohar Lohia Hospital and Atal Bihari Vajpayee Institute of Medical Sciences, New Delhi, India

[3]Head, Department of Respiratory Medicine, Dr Ram Manohar Lohia Hospital and Atal Bihari Vajpayee Institute of Medical Sciences, New Delhi, India

[4]Resident, Department of Respiratory Medicine, Dr Ram Manohar Lohia Hospital and Atal Bihari Vajpayee Institute of Medical Sciences, New Delhi, India

[5]Consultant, Department of Pathology, Dr Ram Manohar Lohia Hospital and Atal Bihari Vajpayee Institute of Medical Sciences, New Delhi, India

[§]Are Considered as Equal Second Authors

***Corresponding Author:** Desh Deepak, Senior Respiratory Physician, Department of Respiratory Medicine, Dr Ram Manohar Lohia Hospital and Atal Bihari Vajpayee Institute of Medical Sciences, New Delhi, India.

Received: October 14, 2021; **Published:** October 27, 2021

DOI: 10.31080/ecprm.2021.10.00880

Abstract

Background and Objectives: Based on the in-vitro studies Hydroxychloroquine sulphate (HCQS) was proposed as a potential therapeutic and prophylactic agent for Covid-19. We conducted a study to evaluate the role of HCQS as a prophylactic agent for Covid-19 among health care workers (HCW).

Methods: HCQS was offered to the HCWs of a tertiary care hospital catering both to Covid and non-Covid patients as a prophylactic agent. HCWs could choose to take or not take HCQS. Cross-sectional questionnaire based online survey was conducted among HCWs to study the HCQS usage and occurrence of covid19. Participants were grouped into HCQ (HCQS users) and non-HCQ (those who did not take HCQS) groups. The two groups were then compared for the occurrence of Covid-19.

Results: Out of 515 health care workers, 278 (54%) used tab HCQS while 237 (46%) did not take it at all. Of those who took, 218 (78% of HCQS users, 42% of total subjects) took HCQS regularly, while 60 (22% of HCQS users, 12% of total) used it irregularly. Out of 515 patients, 22 contracted Covid-19, 15 were HCQS users and 7 were not. No significant association between HCQS use and COVID-19 occurrence was found in our study.

Interpretations and Conclusion: Around half of the healthcare workers used HCQS for prophylaxis of Covid-19. There was no significant difference in the covid-19 positivity among HCQS and non HCQS group; however, the numbers are small for conclusive evidence. As HCQS is known to help in reducing the cytokine storm, the possibility that it helped in controlling the severity of disease cannot be ruled out based on this study. Definitive data from larger randomized controlled trials from a wide array of population groups would be helpful in the forthcoming future with regard to risk-benefit assessment and rational use of HCQS.

Keywords: *COVID-19; Hydroxychloroquine Sulphate; Healthcare Workers; Pre-Exposure Prophylaxis*

Introduction

The world is shaken by the deadly pandemic of COVID-19 ever since it's onset in late December 2019 in the live animal market of Hubei province in Wuhan city, China. It is caused by a novel strain of coronavirus known as SARS-CoV-2 (Severe Acute Respiratory Syndrome

Coronavirus 2) an RNA virus of Coronaviridae family. It was declared a global health emergency in January 2020 by the WHO and pandemic on 11 March 2020 [1]. As of 1st July 2021, there have been 19,10,00,000 confirmed cases of COVID-19 and 41,00,000 deaths globally. There is no known definitive drug for COVID-19 highlighting the importance of its prevention. Prevention can be achieved by avoiding exposure to the virus, vaccination and chemoprophylaxis.

Although vaccines have been developed at an unprecedented pace, it is proving to be very challenging to vaccinate the entire population of the world. Therefore, chemoprophylaxis continues to be an important tool to fight this pandemic especially for high-risk groups like HCWs and frontline workers (FLW). Since development of new drugs required extensive research and time, therefore, repurposing existing medications was a more prompt and economical approach to fulfill a time-sensitive need for effective prophylaxis for healthcare workers who are subject to repeated SARS CoV-2 exposure [2,3]. Many drugs have been proposed for both prevention and therapy for COVID-19 like HCQS, Remdesivir, Lopinavir/Ritonavir, Azithromycin, Ivermectin, Doxycycline, Favipiravir and Steroids [3-10]. Chloroquine has demonstrated *in-vitro* activity against SARS-CoV-2 [4,5]. Studies reported that hydroxychloroquine, a derivative of chloroquine with similar therapeutic effects and fewer adverse effects, is also active against SARS-CoV-2 and may demonstrate relatively greater *in-vitro* viral inhibition [6,7]. In the first study by Gao J., *et al*. it showed significant viral clearance from nasopharynx in COVID-19 patients [3,11,12]. Owing to the tremendous pressure of the pandemic, HCQS was endorsed by many scientific bodies and government agencies because of its easy and widespread availability and known safety profile.

Indian Council of Medical Research (ICMR) was the first medical council worldwide that issued recommendations of deploying HCQS prophylaxis among HCWs and close contacts involved in care of COVID-19 or suspected patients. Given the absence of any conclusive evidence, it also warned against misuse by the general public and included HCQS in schedule H1 of Drugs and Cosmetics Rules, 1945. ICMR advisory expanded the program in May 2020 to include asymptomatic frontline workers (FLW) such as police, paramilitary and the surveillance groups for chemoprophylaxis [13].

Although few studies have shown conflicting results on the efficacy of HCQS as both therapeutic and chemoprophylactic agent yet there is an ongoing interest in the drug for pre-exposure prophylaxis [14]. Even if it is only partially effective, it would be a potent public health tool to decrease the transmission of SARS-CoV-2 and guard frontline workers from Covid-19 infection. Therefore, we sought to determine the effectiveness of Hydroxychloroquine as a pre-exposure prophylaxis agent in the healthcare workers.

Materials and Methods

Study design and patient selection

We conducted an observational case control study by means of a questionnaire circulated through email to health care workers in a tertiary care center in New Delhi (See annexure 1 in supplementary material). There were no institutional guidelines recommending any drug for prophylaxis and HCQS was offered to HCWs as a prophylactic agent purely on a voluntary basis. Through this survey the HCWs were divided into 2 groups i.e. HCQS and non- HCQS groups and the occurrence of COVID-19 in both the groups was determined.

Testing

Incidence was based on the self-reporting of COVID-19 positivity in the questionnaire by the participants where RT-PCR confirmed cases were counted.

Data collection

The questionnaire was evenly distributed among HCWs working in both covid and non-covid areas. This survey contained questions about demographic details, place of work with respect to covid, HCQS intake according to ICMR guidelines (HCQS 400 mg BD on day1 of

week 1, then 400 mg every week for 7 weeks) and adverse effects, Covid-19 illness, symptoms and severity. Incompletely filled forms were excluded. A random 10% forms were telephonically cross-checked for accuracy.

Outcome measures

The main aim of the study is to evaluate the efficacy of HCQS as chemoprophylactic agent in the prevention of COVID-19. Secondary outcome measures were whether the efficacy of HCQS as a chemoprophylactic agent differed among those working in covid areas and those working in non-covid areas, adverse effects of HCQS, and whether or not HCQS prophylaxis decreased the severity of covid 19 illness.

Statistical analysis

Data was analyzed using SPSS version 22 software. Statistical analysis was done by using tests of means of two populations viz. Welch two independent samples t-test, categorical data analysis in the form of contingency tables, partial contingency tables, Chi-squared tests of independence, Chi-squared test of homogeneity, large sample tests of proportion viz. one sample test of proportion and two sample tests for proportions. A p value of < 0.05 was considered statistically significant.

Results

A total of 515 HCWs participated in the study with ages ranging from 20 to 61 years (Figure 1). Out of 205 (40%) personnel in Covid areas, 120 (59%) were currently working in Covid areas (i.e. within the last 14 days) and 85 (41%) had worked in covid areas prior to 14 days. Three hundred and ten (60%) had not worked in a Covid area at all.

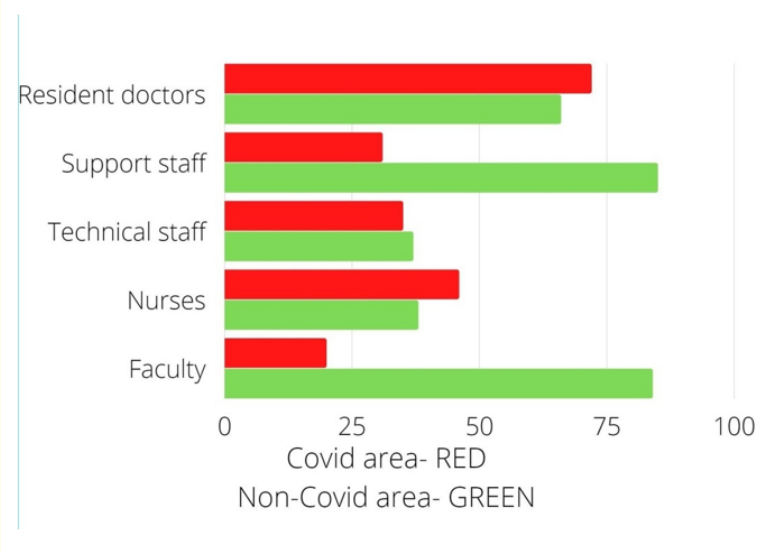

Figure 1: *Distribution of health care workers working in covid and non-covid areas.*

Hydroxychloroquine usage

Out of 515 individuals, 278 (54%) used tablet Hydroxychloroquine while 237 (46%) did not take it at all. Of the 278 subjects who took it, 44 (16%) had taken it for 7 weeks regularly, 171 (61%) were taking it at regular weekly intervals but had not completed 7 weeks and

3(1%) had taken it regularly for more than 7 weeks. Thus 218 (78% of those who took and 42% of total subjects) took Hydroxychloroquine regularly, while 60 (22% of who consumed, 12% of total) used irregularly (Figure 2).

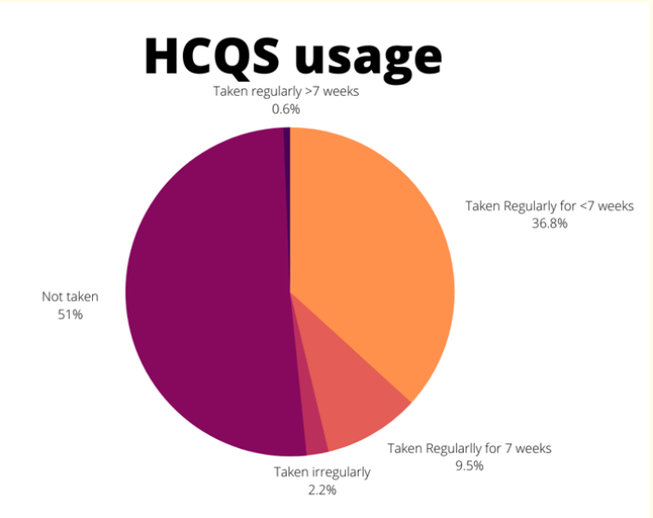

Figure 2: *Pattern of HCQS usage among HCWs.*

ECG was done in 46 (16%) of the 278 subjects using HCQS, though in 3 individuals it was done after starting it. In all these 46 cases ECG was normal. ECG was found to be abnormal in 27 (11%) of the other 237 patients and they had not used HCQS.

Medical comorbidities were found in 112 HCWs. Out of these 53 had not taken HCQS while 59 had taken. On subgroup analysis, 79 worked in non-covid areas while 33 worked in Covid areas. Out of 79 HCWs in non-covid areas, 40 took HCQ while 39 did not take it, making the distribution equal. However, in covid areas distribution was not equal. Out of 33 HCWs with comorbidities in Covid areas 19 (57%) took HCQs while 14(43%) did not take it.

Adverse effects

Thirty seven (13.3%) HCWs had adverse effects with HCQs (Figure 3). Gastrointestinal symptoms, like heartburn, abdominal pain, vomiting and loose stools were predominant. Headache and palpitations were other complaints seen less commonly. Out of 37, 17 (46%) individuals consulted for these effects.

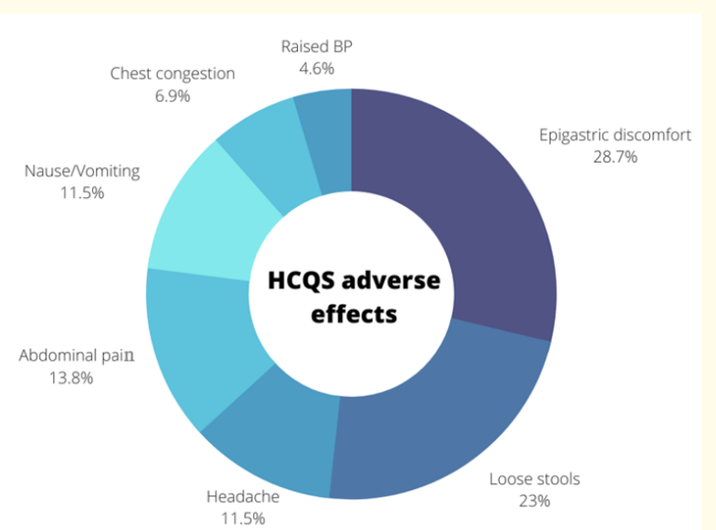

Figure 3: *Frequency of adverse effects with HCQs in HCWs.*

COVID 19 and hydroxychloroquine

Out of 515 HCWs, 493 were negative for Covid-19 while 22 were positive. In covid positive group 15 took HCQS and 7 didn't take HCQS. In covid negative group 263 took HCQS and 230 didn't take HCQS (Table 1).

Group	Covid +Ve	Covid -Ve	Total	P Value
HCQS	15 (5.4%)	263 (94.6%)	278 (53.9%)	0.17
NON HCQS	7 (3%)	230 (97%)	237 (46.1%)	
Total	22 (4.2%)	493 (95.8%)	515 (100%)	

Table 1: *Prevalence of Covid-19 in HCQS and Non HCQS groups.*

Chi square value is 1.86 for df1 with the p value of 0.17 thus implying that there is no significant association between HCQS prophylaxis and Covid 19 positivity.

Out of the 22 positive patients, 12 were asymptomatic and 10 others had mild symptoms. Only one patient in the HCQs group needed oxygen for 1 day.

Out of 205 HCWs working in covid area 13 were positive for Covid 19 and 192 were negative. In the Covid positive group 10 took HCQS and 3 did not take HCQS. In the Covid negative group 123 took HCQS and 69 did not take HCQS.

Out of 310 HCWs working in non covid area 5 were positive for Covid 19 and 301 were negative. In the Covid positive group 5 took HCQS and 4 did not take HCQS. In the Covid negative group 140 took HCQS and 161 didn't take HCQS.

Table 2 summarizes the distribution in the covid and non-Covid areas depicting no statistically significant differences between HCQS and non HCQS groups working in Covid and non-Covid areas for Covid 19 infection.

	Covid area			P value
	Covid +ve	Covid -ve		
HCQS	10	123	133	0.347173
Non HCQS	3	69	72	
	13	192	205	
	Non Covid area			P value
	Covid +ve	Covid -ve		
HCQS	5	140	145	0.592085
Non HCQS	4	161	165	
	9	301	310	

Table 2: *Prevalence of Covid-19 in HCQS and Non-HCQS groups working in covid and non-covid areas.*

Discussion

HCQS is a chloroquine analogue which is commonly used in clinical practice for diseases like malaria, Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus (SLE). It has anti-inflammatory and immunomodulatory action due to inhibition of cytokines such as IL-1,

IL-6, PLA-2 and matrix metalloproteinases. It may help against SARS CoV-2 by decreasing the intracellular pH thereby decreasing iron concentration in the cell which is required by the glycosyl transferase enzyme and thus inhibits terminal glycosylation of ACE-2 enzyme with is the cellular receptor for entry for the virus. The decreased pH also prevents the fusion and uncoating of the virion for viral replication. However, the success of *in-vitro* studies may not translate into clinical efficacy as a specific endosomal concentration of the drug is required or because of other unknown mechanisms.

Adverse drug reactions to HCQS

HCQS in G6PD deficiency patients is linked to increased incidence of hemolytic anemia. It can also cause retinopathy on long term usage, which is usually clinically silent in the earlier stages or it may cause maculopathy in the later stages. Gastrointestinal symptoms with HCQS are common as nausea, vomiting, heartburn and loose stools. Cardiac toxicities such as cardiomyopathy, heart failure, AV black, bundle branch block, QT prolongation especially when administered along with azithromycin have been observed. HCQS has a notorious side effect of causing neutropenia and immunosuppression. In a HCW, taking HCQS can sometimes suppress the immunity and might increase the susceptibility to COVID-19 virus (FDA-2020). FDA also recognized a decreased metabolic activation of the antiviral Remdesivir with concurrent use of HCQS.

There are several trials undergoing to evaluate its efficacy as a pre-exposure prophylactic agent. Various clinical studies evaluating the role of HCQS as a prophylactic agent in COVID-19 management and their limitations are discussed in table 3.

Study Interventions	Study design	Drug regimens and/or doses	Results	Study limitations	Authors
HCQS or Placebo in at risk adults for post-exposure prophylaxis	Double-blind, placebo-controlled RCT. adults who had household or occupational exposure to someone with confirmed Covid-19 (N = 821)	HCQS dose -800 mg once, followed by 600 mg in 6–8 h, then 600 mg daily for 4 days. HCQS, n = 414; Placebo, n = 407	11 subjects in the HCQS arm (2.7%) and 9 in placebo arm (2.2%) had laboratory confirmed COVID-19 (P = 0.82). No significant difference was found; HCQS (11.8%) *vs.* placebo (14.3%), (P = 0.35). HCQS led to more adverse effects (40.1% vs. 16.8%)	Case identification was based on symptoms and not laboratory confirmation; data was obtained by the means of participant reports.	Boulware., *et al*. [17]
HCQS prophylaxis or treatment evidence review	Observational, descriptive population-based study	Dose is 400 mg BD on day 1, followed by 400 mg once every week for 7 weeks.	No compelling evidence for HCQ's use to treat COVID-19, however, it is unsafe to use HCQ in combination with AZM. Unlike antiviral drugs, HCQ has no direct effect on SARS-CoV-2	Small study sample, observer bias, confirmation data not conclusive	Praveen Balabaskaran Nina., *et al*. [18]
HCQS prophylaxis review from articles	Systematic review	PubMed, EMBASE, Clinical trial.gov, International Clinical Trials Registry Platform and Cochrane Library databases were searched for studies that evaluated the prophylactic role of CQ or HCQ on SARS-CoV-2 (pre-clinical studies) or COVID-19 (clinical studies) until 30 March 2020	Although preclinical results are promising, to date there is a dearth of evidence to support the efficacy of CQ or HCQ in preventing COVID-19	No original clinical studies on the prophylactic role of CQ or HCQ on COVID-19 were available.	Sanket Shah., *et al*. [19]

HCQS and CQ prophylaxis	A narrative review of 42 articles	A systematic search of reviews, including in vitro and clinical trial studies in English language focusing on CQ and HCQ effects and adverse effects against COVID-19 in the adult patient population from PubMed was performed.	It is not possible to state the precise efficacy and safety of CQ and HCQ use in the treatment of COVID-19 at any time in the course of the disease. Future studies are warranted.	Lack of information about the treatment and small number of experimental patients, leading to a misinterpretation of the data. Besides, there are few clinical studies with a limited sample size. Moreover, most of them did not present control groups, and some patients had died during these protocols.	Carlos M de Barros., *et al*. [20]
CQ and HCQ prophylaxis or treatment in patients with covid-19	Published studies and rapidly emerging data were reviewed to gather evidence on safety and efficacy of CQ and HCQ in patients with COVID-19 infection or as prophylaxis. The focus is on clinically relevant efficacy endpoints and their adverse effects on QT interval.	The dosing schedules of HCQ in these studies also varied widely as shown in Table 2 in terms of loading dose (range 400-2400 mg), maintenance dose (range 400-800 mg) and duration of maintenance treatment (range 1-14 days). Four studies also reported concomitant treatment with AZM (typically 500 mg on day 1 followed by 250 mg daily for 4 days).	The strategy to repurpose CQ/HCQ to combat COVID-19 infection is overshadowed by concerns about their QT liability, resulting in the choice of potentially subtherapeutic doses. Although the risk of QT-related pro-arrhythmia is real, it is low and manageable by careful monitoring	Observational nature of the study, limited number of published articles reviewed.	Rashmi R. Shah [21]
HCQS prophylaxis in general population and hcw	Reviewed the literature and available data on the prophylactic use of HCQ.	45 (58.5%) CTs have planned a loading dose, while 18 (23.4%) have not; the loading dose is 800 mg in 19 trials (42.2%), 400 mg in 19 (42.2%), 600 mg in 4 (8.9%) and 1,200 mg in 1 (2.2%). Forty trials include at least one daily schedule, while 19 have at least one weekly schedule.	Correct methodological approach is the key to understanding whether prophylactic HCQ can really represent an effective strategy in preventing COVID-19.	Observational study, unavailable information in19.5% CT, not uniform dosing schedule	Manuela Monti., *et al*. [22]

Table 3: *Summary of studies evaluating the role of HCQs as a prophylactic agent.*

Following the review of treatment mortality data, the data safety and monitoring committee recommended continuation of all treatment groups, including resumption of HCQS trial. Subsequently WHO in June 2020 concluded that HCQS did not offer any mortality benefit [16].

We found that only around half of the HCWs used HCQS for the prophylaxis of Covid-19. Our study results demonstrate no protective benefit of pre-exposure prophylactic intake of HCQS against covid 19 irrespective of the covid or non-covid workplace. This result is consistent with results of other studies [2,3,8]. However, there are certain studies which favored HCQS for pre-exposure prophylaxis [9,10]. Both these studies were observational retrospective studies and favorable results could be due to the study being under-powered. Similar to several other studies our study also reported gastrointestinal symptoms as the commonest side effect without any serious adverse effects.

Although there was no significant difference in the two groups, the numbers are small for conclusive evidence. As HCQS is known to help in reducing the cytokine storm, the possibility that it helped in controlling the severity of disease cannot be ruled out based on this study.

Limitations of the Study

Our study is a questionnaire-based study that depended on the understanding of the respondents regarding various questions. However, the respondents were healthcare workers and we randomly cross-checked 10% of the forms telephonically and found them to be correctly filled. There are chances of memory recall bias and possibility of unknown confounders. We could not validate the dose of HCQS taken by participants directly and they were expected to follow ICMR guidelines on HCQS prophylaxis. Adverse effects were self-reported by participants and a contribution of extraneous factors cannot be ruled out. Though ECG was done in a few cases they could not be accessed. Cases were those who were tested positive by RT PCR testing at our institute which does not rule out the possibility of asymptomatic cases among the controls.

Conclusion

Although multiple findings in various studies were positive, these studies had multiple methodological flaws and biases with no controlled comparative groups. HCQS with recent RCT appear to have more hype than hope. HCQS does not appear to offer protection against symptomatic Covid-19 as a pre-exposure prophylactic agent in healthcare workers. However, the numbers in this study are small for a definitive statement and significant adverse effects were not seen with HCQS usage. Possibility of protection against severe covid cannot be ruled out. We would recommend the continuation of large trials on HCQS based pre- and post-exposure prophylaxis to look forward for concrete evidence on its efficacy. It should be ensured that HCQS is used in a controlled setting and close monitoring of patients with COVID-19. This must also not hamper the availability of HCQS for patients with malaria, SLE and rheumatoid arthritis. There must be vigilant monitoring and supervision by authorities on off label use and unreasonable hoarding by the public.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Bibliography

1. Zhu N., *et al*. "A Novel Coronavirus from Patients with Pneumonia in China, 2019". *The New England Journal of Medicine* 382 (2020): 727-733.

2. World Health Organization. WHO (COVID-19) Homepage (2021).

3. Wang M., *et al*. "Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) *in vitro*". *Cell Research* (2020).

4. RECOVERY Collaborative Group Horby P., *et al*. "Dexamethasone in Hospitalized Patients with Covid-19-Preliminary Report". *The New England Journal of Medicine* 384.8 (2021): 693-704.

5. Beigel JH., *et al*. "Remdesivir for the Treatment of Covid-19-Final Report". *The New England Journal of Medicine* 383 (2020): 1813-1826.

6. Cao B., *et al*. "A Trial of Lopinavir-ritonavir in Adults Hospitalized with Severe Covid-19". *The New England Journal of Medicine* 382 (2020): 1787-1799.

7. Caly L., *et al*. "The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro". *Antiviral Research* 178 (2020): 104787.

8. Calder PC., *et al*. "Optimal Nutritional Status for a Well-Functioning Immune System Is an Important Factor to Protect against Viral Infections". *Nutrients* 12.4 (2020): 1181.

9. Oldenburg CE and Doan T. "Azithromycin for severe COVID-19". *Lancet* 396.10256 (2020): 936-937.

10. Yates PA., *et al*. "Doxycycline treatment of high-risk COVID-19-positive patients with comorbid pulmonary disease". *Therapeutic Advances in Respiratory Disease* 14 (2020): 1753466620951053.

11. Liu J., *et al*. "Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro". *Cell Discovery* 6 (2020): 16.

12. Gao J., *et al*. "Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies". *BioScience Trends* 14 (2020): 72-73.

13. Https://www.icmr.gov.in/pdf/covid/techdoc/archive/HCQ_Recommendation_22March.pdf

14. Abella BS., *et al*. "Efficacy and Safety of Hydroxychloroquine vs Placebo for Pre-exposure SARS-CoV-2 Prophylaxis Among Health Care Workers: A Randomized Clinical Trial". *JAMA Internal Medicine* 181 (2021): 195-202.

15. Rajasingham R., *et al*. "Hydroxychloroquine as pre-exposure prophylaxis for COVID-19 in healthcare workers: A randomized trial". *Clinical Infectious Diseases* 72 (2021): e835-e843.

16. https://www.who.int/news/item/04-07-2020-who-discontinues-hydroxychloroquine-and-lopinavir-ritonavir-treatment-arms-for-covid-19

17. Boulware DR., *et al*. "Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19". *The New England Journal of Medicine* 383 (2020): 517-525.

18. Nina PB and Dash AP. "Hydroxychloroquine as prophylaxis or treatment for COVID-19: What does the evidence say?" *Indian Journal of Public Health* 64.S2 (2020): 125-127.

19. Shah S., *et al*. "A systematic review of the prophylactic role of chloroquine and hydroxychloroquine in coronavirus disease-19 (COVID-19)". *International Journal of Rheumatic Diseases* 23 (2020): 613-619.

20. De Barros CM., *et al*. "COVID-19 Pandemic - A Narrative Review of the Potential Roles of Chloroquine and Hydroxychloroquine". *Pain Physician* 23 (2020): S351-S366.

21. Shah RR. "Chloroquine and hydroxychloroquine for COVID-19: Perspectives on their failure in repurposing". *Journal of Clinical Pharmacy and Therapeutics* 46.1 (2021): 17-27.

22. Monti M., *et al*. "Hydroxychloroquine as Prophylaxis for COVID-19: A Review". *Frontiers in Pharmacology* 11 (2020): 605185.

Volume 10 Issue 11 November 2021