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Effectiveness of Prophylactic Drugs for COVID-19 among Healthcare Professionals- A Cross-sectional Observational Study

Pharmacology Section

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ABSTRACT

Introduction: The risk of Coronavirus Disease 2019 (COVID-19) infections among healthcare workers are far greater than those in the general population. A number of prophylactic drugs were being studied during this time for use by the Healthcare Professionals (HCP) who were the first contacts of an infested patient, more so than the general population

Aim: To evaluate the drugs used for pre-exposure prophylaxis for COVID-19 and their efficacy and safety among healthcare workers.

Materials and Methods: A cross-sectional survey was conducted among two hundred and thirty seven healthcare professionals after taking requisite permission from the Institutional Ethics Committee (IHC). A prevalidated survey questionnaire containing 21 questions and an inbuilt consent form was prepared using the Google form. The responses were presented using descriptive statistics of frequency and percentage.

Results: Out of total, 112 (47.26%) participants were on a pre-exposure prophylactic drug, while 125 (52.74%) had not taken any prophylaxis. A total of 19 (16.96%) had used alternative medicine (Ayurveda and Homeopathy). Participants who had taken pre-exposure prophylaxis of modern medicine (n=93), 56 (60.21%) had received Hydroxychloroquine (HCQ) alone or with another drug, and in total 27 (81.8%) had tested negative for COVID-19 infection while on HCQ. Ivermectin which seems to be the other drug which was preferred was taken by 16 participants, three were tested for COVID-19 and two were positive. Only four participants had reported experiencing an adverse drug reaction. Three of them experienced acidity, while on HCQ and one experienced headache, while on ivermectin.

Conclusion: HCQ given in the dose as recommended by Indian Council of Medical Research (ICMR) had significantly reduced the number of infections among HCP.

Keywords: Coronavirus disease 2019, Healthcare workers, Hydroxychloroquine, Pre-exposure prophylaxis

INTRODUCTION

The first human case of COVID-19, caused by the novel coronavirus, subsequently named Severe Acute Respiratory Syndrome (SARS-CoV-2), was first reported by officials in Wuhan City, China, in December 2019 [1]. Coronavirus disease-2019 (COVID-19), was declared as a pandemic by the World Health Organisation (WHO) on March 11, 2020 [2]. More than 204 million people have been infected by the coronavirus whereas more than 2 million people have lost their lives [3]. COVID-19 has exposed health workers and their families to unprecedented levels of risk. Healthcare workers (HCWs) play an essential role, providing care for patients. In the context of COVID-19 and during routine health services, they provide critical care to patients and ensure that infection prevention and control (IPC) measures are implemented and adhered to, in healthcare facilities to limit healthcare-associated infections [4]. The vaccines against COVID-19 have become available but their efficacy and safety was an open question [5]. No definitive treatment was available at that time and the only way to combat this disease was prevention. WHO had issued interim guidance on 19 March 2020 recommending the use of contact and droplet precautions by HCWs caring for patients with COVID-19. WHO encouraged the use of fabric face masks in public places where there is community transmission [6] and where other prevention measures, such as physical distancing, was not possible [7]. Fabric masks, if made and worn properly, can serve as a barrier to droplets expelled from the wearer into the air and environment [7].

Study had shown that coronaviridae infect their target cells by an endocytic pathway. This pathway can be inhibited by chloroquine by reducing their replication. The inhaled virus SARS-CoV-2 likely binds to nasal cavity epithelial cells and replicates here. ACE2 is the main receptor for SARS-CoV-2 as well as SARS-CoV. The virus propagates and migrates down the respiratory tract along the conducting airways, and a final innate immune response is triggered [8].

The authors in a study had given evidence that chloroquine is effective in preventing SARS-CoV-2 infection in cell culture if the drug is added to the cells 24 hour prior to infection. Chloroquine blocks virus infection by increasing endosomal pH required for virus and cell fusion. It also interferes with the glycosylation of cellular receptors of SARS-CoV-2. In addition to this, chloroquine was significantly effective even when the drug was added 3-5 hour after infection. This suggested an antiviral effect even after the establishment of infection and therefore a possible prophylactic and therapeutic use [9]. Studies also suggested that chloroquine/hydroxychloroquine can impair the replication of several viruses other than SARS-CoV-2 by interacting with the endosome-mediated viral entry or by inhibiting the late stages of replication of enveloped viruses [10,11].

It was noted that the clinical worsening of individuals with SARS in week two is related to immunopathological damage and not due to uncontrolled SARS coronavirus replication [11]. Chloroquine/hydroxychloroquine was shown to accumulate in lymphocytes and macrophages resulting in anti-inflammatory properties, and therefore its use in rheumatoid arthritis, lupus erythematosus, and sarcoidosis. An overproduction of tumour necrosis factor α (TNFα) by the alveolar macrophages is the main character of sarcoidosis. Chloroquine (CQ)/hydroxychloroquine (HCQ) reduces the secretion of the proinflammatory cytokines and in particular TNFα, as shown in a murine macrophage cell line seen in a study [11].

Along with Chloroquine, there were other drugs which were also considered for prophylaxis, among these azithromycin, a macrolide antibiotic, Ivermectin an Anthelminthic were found to be likely candidates. Azithromycin is used to treat a very wide range of bacterial and mycobacterial infections of respiratory tract and also skin infections. It had also shown to have antiviral and

anti-inflammatory properties. It has been used as a treatment in previous coronavirus diseases during the epidemics of Severe Acute Respiratory Syndrome (SARS) in 2003 and Middle East Respiratory Syndrome (MERS) in 2012. It was also investigated as a potential candidate treatment for viruses including SARS-CoV-2 [12]. Azithromycin was found to reduce Rhino Virus replication and release during in-vitro infection of Primary Human Bronchial Epithelial Cells (PBEC) [13]. Azithromycin has also been shown to be active in-vitro against Zika virus [14]. Azithromycin and other macrolides also have a number of immuno-modulatory properties and have proven clinical efficacy in a broad range of respiratory diseases including asthma, Chronic Obstructive Pulmonary Disease (COPD), and Diffuse Pan Bronchiolitis (DPB) [15].

However, a retrospective cohort analysis conducted in 2018, of 349 patients across 14 sites in Saudi Arabia found no significant reduction in 90-day mortality or improvement in MERS-CoV RNA clearance with macrolide use [16].

A study done in 2020, using two candidate molecules, hydroxychloroquine and azithromycin, suggested a synergistic inhibition of SARS-CoV-2 replication in vero cells at 5 and 10 μM concentrations, respectively [17]. An approach that this synergy would allow effective use of hydroxychloroquine at less toxic concentrations was tried in a small observational study conducted. It was done to show that these drugs were efficient in clearing viral nasopharyngeal carriage of SARS-CoV-2 in COVID-19 patients in only three to six days [18]. However, there were concerns that combination therapy may enhance cardiovascular side effects as both drugs individually can cause prolongation of the QT interval [19].

In favour of Ivermectin, a meta-analysis of 15 trials found that Ivermectin reduces the risk of death compared with no ivermectin [20].

In patients with suspected COVID-19 in UK, who were at high risk of adverse outcomes, treatment with doxycycline was not associated with clinically meaningful reductions in time to recovery or hospital admissions or deaths related to COVID-19, and should not be used as a routine treatment for COVID-19 [21].

A retrospective case-control analysis at ICMR had also found that there is a significant dose-response relationship between the number of prophylactic doses taken and frequency of occurrence of SARS-CoV-2 infection in symptomatic healthcare workers who were tested for SARS-CoV-2 infection [22].

Indian Council of Medical Research, therefore recommended the use of HCQ in all asymptomatic healthcare workers involved in containment and treatment of COVID-19 and asymptomatic healthcare workers working in non COVID-19 hospitals/non COVID-19 areas of COVID-19 hospitals/blocks as well as amongst the asymptomatic frontline workers, such as surveillance workers who were deployed in containment zones and paramilitary/police personnel involved in COVID-19 related activities. Dosage recommended was 400 mg twice a day on day 1, followed by 400 mg once weekly for next seven weeks which was to be taken with meals. The experts at ICMR further recommended for its use beyond eight weeks on weekly dosage with strict monitoring of clinical and Elecrocardiogram (ECG) parameters under supervision. Further, for reducing any adverse effects ICMR had recommended that an ECG (with estimation of QT interval) to be done before prescribing HCQ prophylaxis, an ECG in case any new cardiovascular symptoms occurs (e.g palpitations, chest pain syncope) during the course of prophylaxis, an ECG (with estimation of QT interval) in those who are already on HCQ prophylaxis before continuing it beyond eight weeks. Atleast one ECG should be done anytime during the course of prophylaxis. Along with hydroxychloroquine, healthcare workers and other frontline workers on HCQ were also advised to use Personal Protective Equipmemt (PPE) in accordance with the guidelines issued by the Ministry of Health and Family welfare [22].

This study was therefore done, to understand the pattern of prophylactic drug usage, preference of the drug and effectiveness of drugs used for COVID-19 for prevention among HP.

MATERIALS AND METHODS

The present cross-sectional observational study was conducted in February 2021, after taking a proper informed consent, among healthcare professionals which included doctors, nurses, and interns, after requisite approvals from the Institutional Ethics Committee (Approval number–TMCHRC/IEC/003).

Inclusion criteria: HCWs including doctors, nurses, interns working in direct or indirect contact with COVID-19 infected patients.

Exclusion criteria: Janitors, pregnant staff working in direct or indirect contact with COVID-19 infected patients Incompletely filled forms.

Study Procedure

A survey questionnaire in English was developed after literature review and discussion with healthcare workers, regarding the drugs which were being used for prophylaxis. The developed questionnaire was evaluated by experts from different disciplines for content validation. It was divided into four parts:

1) Questions regarding the Sociodemographic details of the participants consisting of age, gender, place of residence and Institute/hospital, designation, whether the hospital was a tertiary care hospital or a private hospital, whether it was a dedicated COVID-19 hospital or not.
2) This part was regarding the prophylactic drugs being taken by them. These were open ended questions, where they were expected to fill out the details of the name, dose and duration of drugs. Since they were medical professionals there was a likelihood that they were taking the drugs after doing their own research or getting them from institutes which were following ICMR guidelines. Hence, the question whether the drugs were prescribed by ICMR or by the Institute or by self was added.
3) Had questions whether they experienced any adverse drug reactions.
4) In the questions regarding COVID-19 testing, whether they tested positive or negative during the period they were on the prophylactic drug was asked, along with this whether they were taking any alternative medicine (Ayuveda/Homeopathy) for prophylaxis, as these were also rampantly used. There was an open ended question to share any other information which was relevant to the present study.

The confidentiality of the participants was maintained. The questionnaire was distributed through Gmail, WhatsApp, and Instagram as a Google form with the informed consent being the compulsory part to be answered. The time required to complete the Google form was estimated to be 4-5 minutes.

STATISTICAL ANALYSIS

The data collected was tabulated in an Excel sheet and the responses were presented using descriptive statistics of frequency and percentage.

RESULTS

A total of 237 participants completed the survey. Of these 90 (37.97%) were females and 147 (62.02%) were males. As depicted in [Table/Fig-1], 76 (32.07%) participants were of the age group 41-50 years and 57 (24.05%) were between the age groups of 31-40 years. The eldest was 75 years old and the youngest was 22 years old.

[Table/Fig-2] shows the region of the participants, 209 (88.19%) participants were from Mumbai and Navi Mumbai regions. Most of our participants 201 (71.44%) were practicing doctors. About 146 (61.60%) of study participants worked in primary care clinics while 91 (38.39%) were providing service in tertiary care hospitals.

As shown in [Table/Fig-3], 135 (56.96%) were practicing in a private clinic. Out of the 237 participants, 170 (71.73%) of the participants were involved in providing direct or indirect care to the COVID-19

Age (in years)	n (%)
21-30	45 (19%)
31-40	57 (24.05%)
41-50	76 (32.07%)
51-60	39 (16.46%)
>61	20 (8.44%)
Total (n)	237

[Table/Fig-1]: Age-wise distribution of the participants.

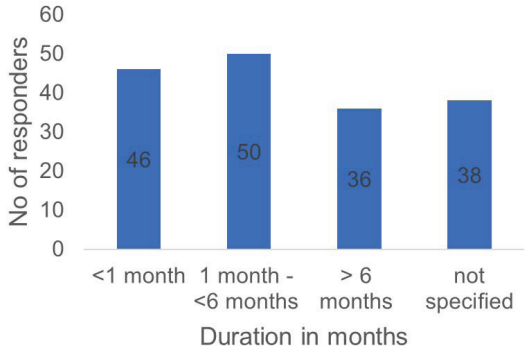
Region of the participants	n (%)
Mumbai	169 (71.30%)
Navi Mumbai	40 (16.88%)
Satara	1 (0.42%)
Akola	1 (0.42%)
Ratnagiri	1 (0.42%)
Pune	1 (0.42%)
Telangana	18 (7.59%)
Indore	1 (0.42%)
Punjab	1 (0.42%)
Gujarat	3 (1.27%)
Kolkata	1 (0.42%)
Total	237

[Table/Fig-2]: Distribution of the region of the participants.

Place of work	n (%)
Private clinic	135 (56.96%)
Dedicated COVID-19 hospital	91 (38.4%)
Receiving both normal and COVID-19 patients	11 (4.64%)
Total	237

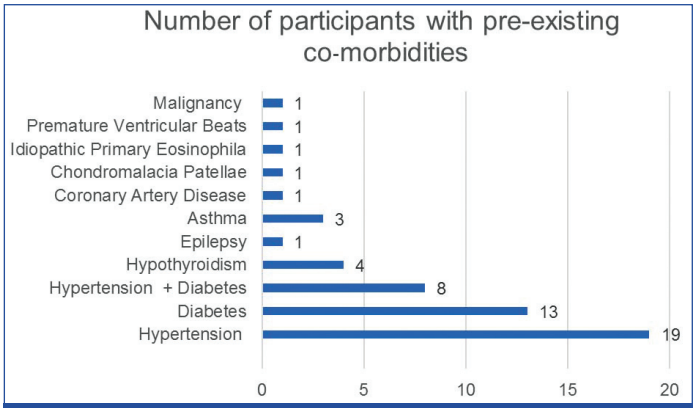
[Table/Fig-3]: Distribution of the participants depending on their place of work.

patients and 67 (28.27%) were not seeing COVID-19 patients on a regular basis. Of the participants, who were providing care to COVID-19 patients, 50 (29.41%) participants had provided for a period of six months, whereas 36 (21.18%) had provided for more than six months as shown in [Table/Fig-4].



[Table/Fig-4]: Bar chart showing duration in months, of direct or indirect care provided by the HCP to suspected or confirmed cases of COVID-19 infection.
*More than 6 months indicated the time up to 1 year as it was difficult to predict the waves most of them had continued taking the prophylactic drug.

In total, there were 53 (22.36%) participants with co-morbidity as shown in [Table/Fig-5], of these the most common co-morbidity was hypertension with 19 (35.85%) participants and 13 (24.53%) participants had diabetes mellitus. Information regarding the drugs used by the participants with co-morbidities is shown in [Table/Fig-6]. Some other drugs like steroids, bronchodilators and anti-platelet drugs were also used, but their names were not mentioned. Also the dose of the drugs were not mentioned by the participants.



[Table/Fig-5]: Distribution of the participants according to their co-morbidity (Those with more than one co-morbidity were included in all groups separately).

Drug class	Name	n (%)
Beta blocker	Metoprolol	5 (8.77%)
Tyrosine kinase inhibitor	Imatinib	1 (1.75%)
Anti-convulsant	Phenytoin	1 (1.75%)
Thyroid hormone	Levothyroxine	3 (5.26%)
Biguanide	Metformin	14 (24.56%)
Sulfonylurea	Glimepiride	4 (7.015)
	Gliclazide	1 (1.75%)
Dipeptidyl peptidase-4 inhibitor	Vildagliptin	1 (1.75%)
	Tenegliptin	1 (1.75%)
Angiotensin Receptor Blocker	Telmesartan	15 (26.315)
	Olmesartan	2 (3.50%)
Calcium channel blocker	Amlodipine	3 (5.26%)
	Cilnidipine	3 (5.26%)
Angiotensin converting enzyme inhibitor	Pirindopril	1 (1.75%)
Thiazide diuretic	Indapamide	1 (1.75%)
Alpha glucosidase inhibitor	Voglibose	1 (1.75%)
Total	Total	57

[Table/Fig-6]: Drugs used by participants with co-morbidities.

Among the participants, 112 (47.26%) had taken the pre-exposure prophylactic drug while 125 (52.74%) had not taken any prophylaxis. Among them 80 (71.43%) were taking the drug following the ICMR guidelines, 49 (43.75%) of these participants were directly following guidelines issued by ICMR, 14 (12.5%) received the prophylactic drug distributed by the hospital, and 17 (15.17%) consulted some doctor. Thirty two (28.57%) self-prescribed the drug following online research.

Among the 112 participants who had taken pre-exposure prophylaxis for COVID-19, 19 (16.96%) had used alternative medicine (Ayurveda and Homeopathy). Of the participants who had taken modern medicine (n=93), in total 56 (60.21%) had taken hydroxychloroquine in the dose of 400 mg twice a day on Day 1, followed by 400 mg once weekly for next seven weeks. Out of these, 52 (92.85%) participants had taken it alone and 3 (5.35%) responders had taken it in combination with Ivermectin (12 mg once a week) and 1 (1.78%) had taken it with azithromycin (500 mg once daily, duration not specified). Of these only three participants had said they experienced an adverse drug reaction that too only acidity and 2 among them had taken antacid for the ADR. Ten (10.75%) participants had taken ivermectin (12 mg once weekly or Ivermectin 12 mg twice a day for four days) either alone, or in combination with multivitamins (once a day), 5 (50%). Among the people who had taken ivermectin, one participant had experienced an adverse drug reaction, headache and had taken paracetamol for the same.

Seventeen (18.27%) participants said they had taken multivitamin once daily. Ten (10.75%) participants had taken azithromycin either alone, or along with other drugs like ivermectin, 3 (30%), doxycycline 1 (10%) and favipiravir 1 (10%), of these three underwent test for

COVID-19 and two were positive. Most of the participants had mentioned that they had taken vitamin C, vitamin D3 and zinc along with multivitamins. They had not specified the dose of these drugs. One participant had taken favipiravir (dose not specified) along with azithromycin and one had taken it alone. One participant had taken oseltamivir 75 mg twice a day for seven days.

As shown in [Table/Fig-7], of the 112 participants who had taken the pre-exposure prophylaxis, 56 (50%) had undergone a test for COVID-19, and among them 22 (39.29%) were tested positive. Out of the 125 participants who had not taken any prophylaxis, 43 got tested for COVID-19 during their work, and 20 (46.51%) were positive for SARS-CoV-2.

As seen in [Table/Fig-8], 52 participants were taking hydroxychloroquine which was the most common prophylactic drug consumed and among these participants, 33 (63.46%) got tested for COVID-19 and 27 (81.81%) were tested negative. Among the participants, who were taking ivermectin only one got tested and that person tested positive.

Variables	Participants who had taken pre-exposure prophylactic drug n (%)	Participants who had not taken pre-exposure prophylactic drug n (%)
Tested Positive	22 (39.29%)	20 (46.51%)
Tested Negative	34 (60.71%)	23 (53.49%)
Total number of people who underwent COVID-19 test result	56	43

[Table/Fig-7]: Distribution as n (%) participants who underwent COVID-19 test, who had/had not taken pre-exposure prophylaxis.

Drug	No. of HCWs	No. of HCWs who got tested for COVID-19	Result	
			Positive	Negative
Azithromycin	5	2	2	0
Azithromycin+Ivermectin	3	0	0	0
Azithromycin+Doxycycline	1	1	0	1
Azithromycin+Favipiravir	1	0	0	0
Hydroxychloroquine	52	33	6	27
Hydroxychloroquine+Ivermectin	3	0	0	0
Hydroxychloroquine+Azithromycin	1	0	0	0
Ivermectin	5	1	1	0
Ivermectin+Multivitamins	5	2	1	1
Multivitamin	17	7	4	3
Others	19	10	8	2
Total	112	56	22	34

[Table/Fig-8]: Result of COVID-19 test of the participants while on pre-exposure prophylactic drug, comparison between drugs indicating their efficacy.

DISCUSSION

Throughout the pandemic, it was seen that the previously done research by using already available drugs in the market to inhibit the virus was the first step. Most of these drugs were found to have action in-vitro, but whether this will be same in-vivo, was the question that needed to be answered.

In a study conducted by Chatterjee P et al., in 2020, they found benefits of HCQ prophylaxis in SARS-CoV-2 infection (COVID-19). It was also mentioned that simply taking HCQ prophylaxis did not reduce the number of SARS-CoV-2 infections among healthcare workers, but after the intake of four or more maintenance doses of HCQ, the protective effect was observed. The authors mentioned that in the adjusted multivariate model, a significant reduction (>80%) in the odds of SARS-CoV-2 infection in the HCWs was seen with the intake of six or more doses of HCQ prophylaxis [23]. Another study conducted by Bhattacharya R et al., demonstrated that consumption of HCQ as prophylaxis among high risk individuals was associated with a significantly reduced risk of testing positive for COVID-19 [24]. This was reflected in the survey done by the authors, HCQ was the major drug which was recommended and preferred by HCP. HCQ according to this paper is significantly associated with reduction in the number of positive cases (27 out of 33, 81.81%) as compared to the 43 participants out of 125, who were not taking any prophylactic drug and who underwent COVID-19 test, 23 (53.49%) were negative.

Along with potential antiviral property, HCQ is also known to have anti-inflammatory properties, together with the low cost of therapy and excellent oral bioavailability, high tissue concentrations in the lungs relative to the plasma levels and acceptable safety profile [25] make this, a drug which can be studied further for use in pandemic situations, as it requires large quantities of drug distribution.

A study done in September to October 2020 in Bhubaneshwar, the participants were selected depending on their intake of ivermectin and/or hydroxychloroquine and/or vitamin-C and/or other prophylaxis for COVID-19.They concluded that two-dose ivermectin prophylaxis at a dose of 300 µg/kg with a gap of 72 hours was associated with a 73% reduction of SARS-CoV-2 infection among healthcare workers for the following month [26]. In the present study 16 participants only, in total, had taken ivermectin in the dose of 12 mg weekly alone or with other drugs, and three were tested for COVID-19 and two were positive. Ivermectin in the present study was over shadowed by HCQ which seems to be the preferred drug for prophylaxis.

Although chloroquine/hydroxychloroquine were the main recommended drugs for prophylaxis, and others like azithromycin, doxycycline and ivermectin were at that time used for treatment of mild and moderate COVID-19 disease. The participants receiving alternative therapy (Ayurveda and Homeopathy) were not included, while calculating the efficacy or safety of the drugs, as the authors do not have the required expertise in these fields.

Limitation(s)

This study had a drawback, as the preference for prophylactic drugs changes regionwise. Secondly, the population studied in this study was more of interns and residents which does not reflect the entire population of HCW.

CONCLUSION(S)

HCQ given in the dose as recommended by ICMR had significantly reduced the number of infections among healthcare professionals. Ivermectin, also another promising candidate for prophylaxis requires more study as in present case, the sample was small to conclude in its favour. However, being antibiotics of relevance it is always necessary to keep in mind that there are chances of development of drug resistance.

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