Original Research Article

A Retrospective Study on Pre Exposure Hydroxychloroquine and Ivermectin Prophylaxis for COVID-19 in Healthcare Workers in a Tertiary Care Hospital

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Abstract

Background:COVID-19 was declared a 'pandemic' by the WHO on 11th March, 2020. The high infectivity and unique transmission potentials of the causative agent of COVID-19, namely, SARS-CoV-2 were the reasons behind its wide-scale spread and made health care workers (HCWs), the most 'at-risk population' for acquiring the infection.The administration of HCQs and/or Ivermectin prophylaxis was one of the most commonly used stratagems recommended to protect the HCWs prior to the development of an effective vaccine. But data on its effectiveness, if any, were not conclusive. Also the above strategy was not accepted by many HCWs themselves for a plethora of reasons. Hence a systematic enquiry into the above conundrums was felt to be the need of the hour. **Objective:** 1.To assesses the effectiveness of HCQs and Ivermectin as pre-exposure prophylaxis (PrEP) drugs against SARS-CoV-2 infection among HCWs in a tertiary care hospital. 2. To identify the reason(s) behind avoidance of PrEPamong HCWs. **Materials and methods:** We conducted a retrospective study based on an online/ offline/ telephonic survey on HCWs directly related to COVID care services. **Results:** Total 336 HCWs responded to our survey. There were segregated intotwo cohort groups, namely, those taking PrEP (n=148; exposed) and those avoidingPrEP (n=188; control). In the PrEPgroup, 26 (17.56%) out of 148 participants reported to have tested positive for SARS-CoV-2 during some point of time, whereas, in the control group, 38 (20.21%) out of 188 participants reported to have been SARS-CoV-2 positive. We found no significant reduction SARS-CoV-2 cases in exposed group with relative risk of 0.8691 (95% Confidence Intervals 0.5542 to 1.363, *p <0.3181*).**Conclusions:** Our study demonstrated that voluntary consumption of PrEP by HCWs is not associated with a statistically significant reduction in risk of SARS-CoV-2.

Keywords: SARSCoV-2, Hydroxychloroquine, Ivermectin, pre-exposure prophylaxis, healthcare workers

Background

The novel coronavirus disease (COVID-19) was recognised as a 'disease' around December 2019 in Wuhan, China and spread to more than 200 countries within five months. The WHO declared it as pandemic on 11th March, 2020. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is the causative agent of this disease. It can spread efficiently through respiratory droplets and contact routes[1-4]. Patients commonly presented with fever, fatigue, dry cough, myalgia, dyspnoea and new-onset anosmia or ageusia. Less commonly few patients reported having diarrhoea, nausea and vomiting.

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Majority of the SARSCoV-2 infected individuals (around 80%) did not have any noticeable symptoms and yet were able to transmit the infection[5]. Such unique transmission potentials of SARS-CoV-2 and lack of definitive antiviral therapy were the reasons behind its wide-scale spread. Evidence indicates that healthcare workers (HCWs) are particularly at risk of acquiring SARS-CoV-2 infection, due to repeated occupational exposure[6].

As there is no specific treatment against COVID-19, social distancing, use of face masks and frequent hand washing with soap or alcohol based hand rubs constituted the infection prevention measures for general population[7-9]. Being exposed to a higher quantum of risk, HCWs needed additional intervention approaches for protection[10]. Aprons, gowns, gloves, masks, face shields and goggles addressed such needs but only partially. The development of a safe and effective vaccine against SARS-CoV-2 has been the quest of the scientific community ever since the emergence of COVID 19 as it would obviously provide the most effective protection. Their efforts has started to bear fruit only recently in the form of a few vaccines. However during the 'latent period' between emergence of COVID 19 and vaccine availability there was obvious need to have effective

additional alternative strategies for preventing COVID-19 among the health care workers. Chemoprophylaxis, which hadin the past demonstrated to be a successful modality in preventive medicine for a number of other infectious diseases like malaria, HIV and influenza was considered to have the potential to cover this additional risk.

A number of clinical trials were undertaken to test the efficacy of several repurposed drugs like Chloroquine (CQ), Hydroxychloroquine (HCQ), Ivermectin, Remdesivir, Ritonavir/Lopinavir for prophylaxis as well as treatment of COVID-19[11]. None have so far shown exceptional results[12,13,14].Of these, although HCQs has gathered particular worldwide attention based on in vitro results demonstrating efficacy against SARS-CoV-2, there is lack ofevidence to suggest that HCQ offers any significant additional clinical benefit for the treatment of hospitalised COVID-19 patients.

In this study we have chosen to focus on the roles of Hydroxychloroquine and Ivermectin in prevention of COVID-19 among health care workers.Hydroxychloroquine (HCQ), which is a derivative of Chloroquine (CQ), is an immunomodulator and has exhibited in vitro potent antiviral properties against various viruses[15]. Ability of this compound to inhibit the infection by SARS-CoV-2, as well as viral replication in cell cultures in a time- and dose-dependent manner made it a primary choice[16]. Furthermore, HCQ elevates the pH of endosomes and inhibits SARSCoV-2 RNA-mediated inflammatory response[17]. These laboratory findings encouraged researchers to consider HCQ, originally used for malaria, as a repurposed agent for prophylaxis against SARS-CoV-2[18].

Recently three studies of HCQ prophylaxis in health care workers (HCWs) from India reported encouraging results. One cohort study found that 38% of untreated HCWs developed COVID-19 infection compared to 7% of HCWs treated with weekly HCQ PrEP (*p<0.001*)[19]. The second case–control study of HCWs found that four or more weekly doses of HCQ resulted in significantly less infection with SARS-CoV-2 (adjusted odds ratio 0.44, *p<0.001*)[20]. The third study was a questionnaire-based analysis showing that HCWs who had taken a full course of HCQ PrEP (seven or more weekly doses) had significantly less infection with SARS-CoV-2 compared to those who had taken either an incomplete course or no HCQ at all (*p = 0.021*)[21]. Additional clinical observations suggest that HCQ PrEP may be effective for COVID-19. In a multicentric retrospective study of 6,228 rheumatic disease patients from China, patients who were taking HCQ had a lower risk of SARS-CoV-2 infection compared to patients taking other disease-modifying anti-rheumatic drugs (odds ratio 0.09, *p=0.044*)[22]. Another population-based analysis of over 360,000 subjects from Portugal found that chronic HCQ treatment was associated with a significant decrease in SARS-CoV-2 infection (adjusted odds ratio 0.51, *p=0.04*)[23]. ICMR published guideline on HCQS prophylaxis on 23rd March 2020[24].

Vora A *et al* told that another option is the antiparasitic drug Ivermectin[25] which has antiviral activity also. It is effective against SARS-CoV-2 in vitro and in vivo[26-29]. It is act by sequestering SARS-CoV-2 viral nucleocapsid protein (NCP) into the host nucleus through the nuclear-pore-complex which is a vital step in viral pathogenesis and defence against host immune response[30]. Ivermectin selectively inhibits host importin α/β transporter protein which decreases translocation (shuttling) of SARS CoVnucleocapsid protein (NCP) from the cytoplasm to the nucleus, altered NCP distribution disrupts viral propagation & survival[31]. The half-life of Ivermectin is 12–36 hours in humans, and its metabolites may persist for up to 12 days due to high lipid solubility. It can be dosed daily or weekly at 0.15–0.2mg/kg with minimal side effects, but clinical PrEP trials for COVID-19 using Ivermectin have not been organized to date, and appropriate antiviral dosing remains questionable[32]. Individuals with specific gene mutations may have adverse reactions to Ivermectin[33].

However, data on its prophylactic role is still incomplete. This retrospective cohort study explores the usage of HCQ and Ivermectinin a tertiary health care centre in India amongst healthcare workers and investigates its prophylactic potential in prevention of COVID-19 infection.

Objectives

1. To assess the effectiveness of HCQ and Ivermectin as pre-exposure prophylaxis(PrEP) against SARS-CoV-2 infection among health care workers (HCWs) in a tertiary care hospital.
2. To identify the reasonsfor avoidance of pre-exposure prophylaxis

Materials and methods

We conducted a retrospective study based on an online/ offline/ telephonic survey on health care personnel, who are working at College of Medicine Sagore Dutta Hospital, Kolkata, a tertiary care teaching hospital in India, dealing with COVID-19 patients. HCWs who had voluntarily taken chemoprophylaxis by HCQ or Ivermectin prior to exposure were considered one cohort while those who had not taken any prophylaxis were considered to be the control group.

Study type & design

This is a retrospective cohort study based on an online/ offline/ telephonic survey on health care personnel, who are working at College of Medicine Sagore Dutta Hospital, Kolkata

Study setting

Department of Microbiology, College of Medicine and Sagore Dutta Hospital

Study period

1st January – 31st January 2021

Study population

HCWs of College of Medicine and Sagore Dutta Hospital directly related to Covid care services (both treatment and diagnosis)

Inclusion criteria

HCW (directly related to Covid care services) voluntarily taking HCQS and/ or Ivermectin

Exclusion criteria

Refusal to give consent for the study,

Sample size

As per considering two sided confidence interval 95%, power 80%, 1:1 exposed and unexposed ratio and assuming 54.5% (from the study done by Bhattacharya R *et al*) unexposed developed Covid-19 after exposure [19] the sample size was calculated using Open Epi software version 3.01. Sample size found to be minimum 143 per group.

Sampling method

Two groups identified – HCWs who had voluntarily taken chemoprophylaxis by HCQ or Ivermectin prior to exposure were considered one cohort (exposed) while those who had not were considered to be the control group.

Tools and techniques

Questionnaire based study

Methods of data collection

It is a retrospective cohort study where participants volunteered to provide data either on an online/ offline form or over the telephone

Plan for data management and analysis

Proportion was expressed in percentage. The risk ratio was calculated to assess the effectiveness of HCQ and Ivermectin as PrEP against SARS-CoV-2 infection among in health care workers. To find out association between SARS-CoV-2 positivity and PrEP intake chi-square test is used. Calculation was done by Open Epi software version 3.01. A *p value < 0.05* is considered statistically significant.

Ethical considerations

Study was commenced after receiving approval from Institutional Ethics Committee (IEC). The study was conducted in conformity with all ethical guidelines. Only those persons willing to participate in the study and sign an informed consent form was be included. Identity of all the study subjects were kept confidential

Implications

To explore the effectiveness of HCQS and/orIvermectin as PrEP for COVID 19 among health care workers

Results

We were questioned HCWs of College of Medicine and Sagore Dutta Hospital directly related to Covid care services (both treatment and diagnosis). Among them, 336 participants responded. Out of 336 HCW, 148 (44%) were taking pre-exposure (PrEP) and 188 (55.9%) were not taking any pre-exposure prophylaxis.

Out of 336 HCW, 163 (48.5%) were doctors, 76 (22.6%) were nurses, 49 (14.5%) were medical technologists (MT) and 48 (14.2%) were general duty assistants (GDA). Among 336 participants, 178 (52.9%) were male and 162 (47%) were female.

Among 148 HCW taking PrEP18 (12.1%) took both HCQS and Ivermectin, 92 (62.2%) took only HCQS, 12 (8%) took only Ivermectin and 26 (17.56%) took previously HCQS and now Ivermectin.

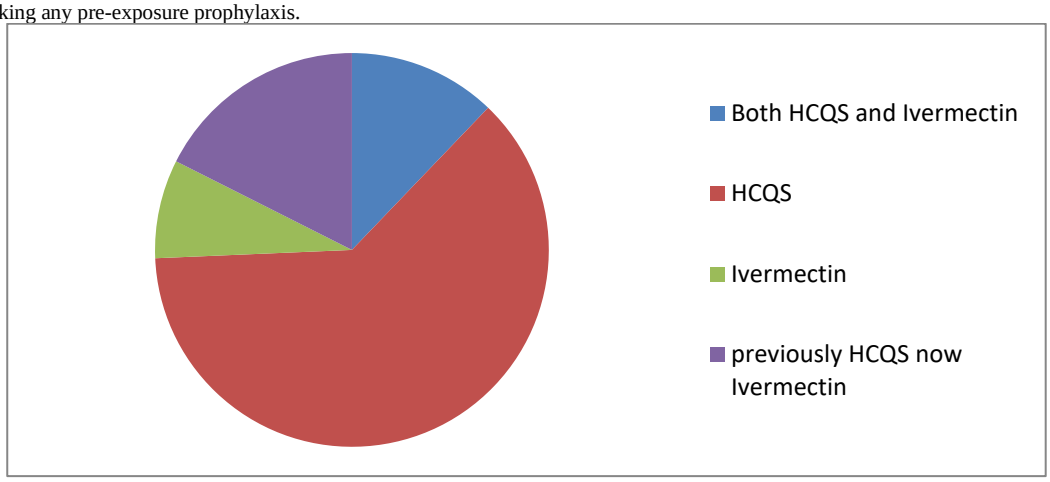

Fig 1: Distribution of pre-exposure prophylaxis among HCW

The two cohort groups of those taking PrEP (henceforth mentioned as exposed)and those not takingPrEP(henceforth mentioned as control) were comparable in respect to age, sex and risk of exposure to Covid 19. In the pre-exposure prophylaxis group (exposed) 26(17.56%) out of 148 participants were tested to be SARS-CoV-2 positive, whereas, inthe control group 38(20.21%) out of 188 participants were found to be SARS-CoV-2 positive.

Table 1: Distribution of SARS-CoV-2 positive cases among pre-exposure prophylaxis taken group and pre-exposure prophylaxis non-taken group

Study Groups	SARS-CoV-2 positive	SARS-CoV-2 negative	Total
Pre-exposure prophylaxis taken (exposed)	26	122	148
Pre-exposure prophylaxis not taken (control)	38	150	188
Total	64	276	336

Risk in Exposed - 17.57%(95% Confidence Intervals 12.23 to 24.55); Risk in Unexposed 20.21%(95% Confidence Intervals 15.07 to 26.55); Overall Risk - 19.05% (95% Confidence Intervals 15.19 to 23.6); Risk Ratio - 0.8691 (95% Confidence Intervals 0.5542, to 1.363); Prevented fraction in exposed(PrEPtaken group) only 13.09% (95% Confidence Intervals 36.3 to 44.58).

Further analysis of incidence of infection between the two groups demonstrated that theincidence of SARS-CoV-2 in those on HCQ pre-exposure prophylaxis was significantly lesswhen compared to the control group with a $\chi 2$ value of 0.2238 $p < 0.3181$ which is not significant. So in our study there is no significant reduction in SARS-CoV-2 in PrEPexposed group.Reasons for avoidingpre-exposure prophylaxis were: allergy – 12 (6.3%), breast feeding – 5 (2.6%), cardiac problem – 6 (3.2%), fear of side effects – 31 (16.4%), not sure about efficacy – 37(19.6%), not known – 87 (46.2%), pregnancy – 4 (2.1%), eye problem – 6 (3.2%).

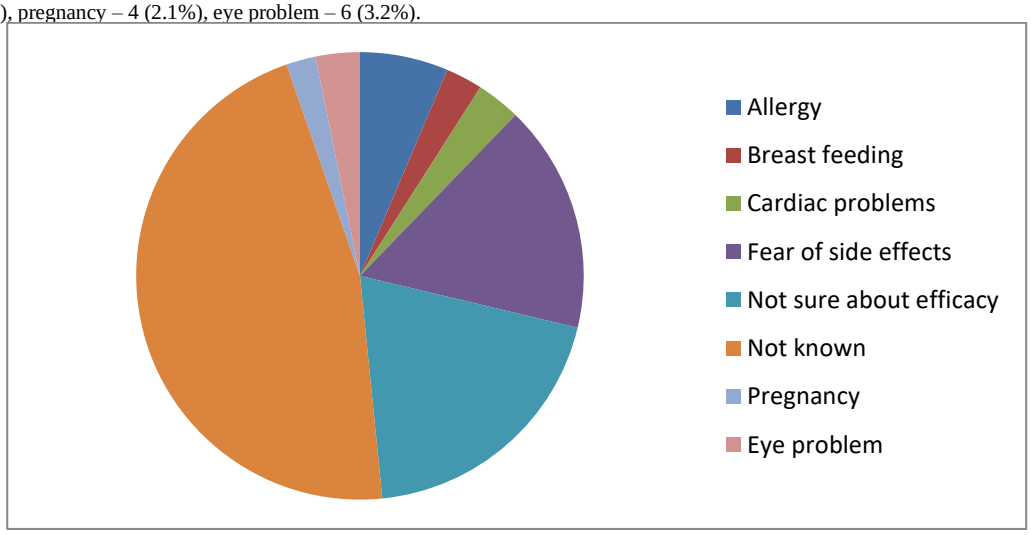

Fig 2: Distributions of reasons behind not taking pre-exposure prophylaxis

Out of 148 HCW taking pre-exposure prophylaxis, most of them reported mild adverse effects. Among them 8(5.4%) reported headache, 6(4.05%) reported dizziness,26 (17.56%) reported gastrointestinal side effects (diarrhoea, abdominal cramps, nausea and vomiting) and 12(8.1%) reported skin rash. 96(65%)did not complain ofany side effects.

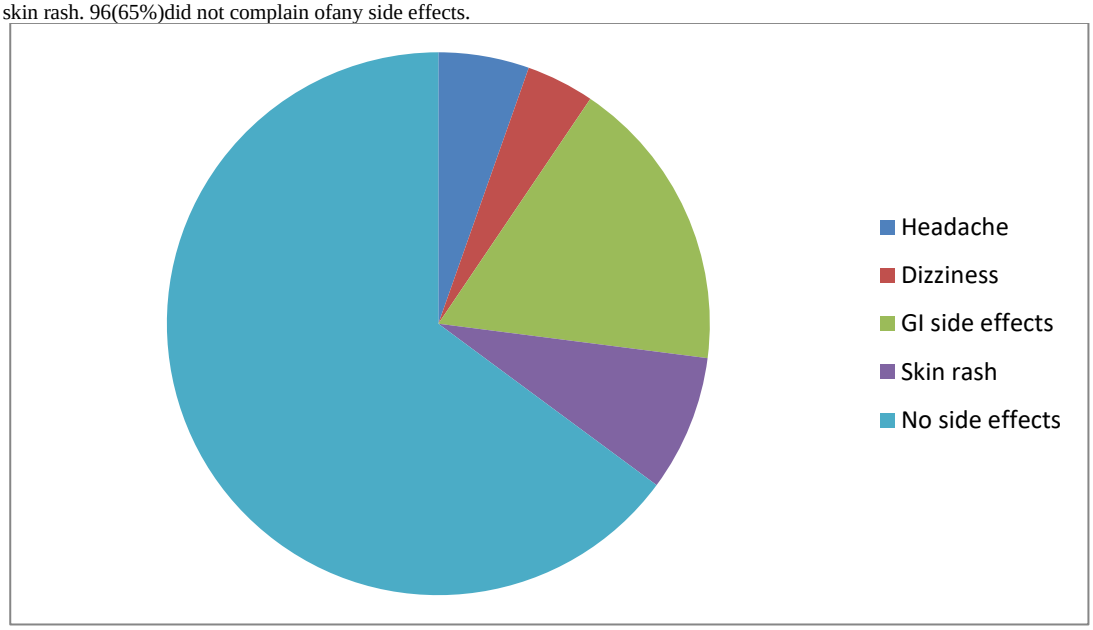

Fig 3: Distribution of side effects among HCW

Discussion

Our study aimed to investigate the effectiveness of pre-exposure prophylaxis (PrEP) among health care worker (HCW).

In this study 12.1% HCW took both HCQS and Ivermectin, 62.2% took only HCQS, 8% took only Ivermectin and 17.56% HCW took previously HCQS now Ivermectin. We didn't find any similar data to compare.

There were 26SARS-CoV-2 cases (17.56%) among HCWs taking pre-exposure prophylaxis (n=148) (exposed group), while there were 38 (20.21%) SARS-CoV-2 cases among the HCWs not taking PrEP(n=188) (control), with a relative risk of 0.8691 (95% Confidence Intervals 0.5542 to 1.363,*p <0.3181*), indicating that though there is reduction of SARS-CoV-2 cases among exposed group there was no significant reduction of SARS-CoV-2 cases among HCW taking pre-exposure prophylaxis. Our finding is not similar to the finding of Bhattacharya R *et al* [19] and Behera P *et al* [34]. They found significant reduction of SARS-CoV-2 cases among HCW taking pre-exposure prophylaxis. However, Rajasingham R *et al*documented in there randomised control trial that there is no significant reduction of SARS-CoV-2 cases in HCW following pre-exposure prophylaxis use[35].Most of the HCW didn't took post-exposure prophylaxis due to unknown reason (46.2%), 19.6% were not sure about efficacy, 16.4% due to fear of side effects. Others are due to allergy (6.3%), breast feeding (2.6%), cardiac problem 3.2%, pregnancy 2.1%, and eye problems 3.2%. There were no similar data to compare.

Out of 148 HCW taking pre-exposure prophylaxis, most of them reported mild adverse effects. Most common side effects are gastrointestinal (17.56%) similar to the study done by Bhattacharya R *et al*[19].

Conclusion

Our study demonstrated that voluntary consumption of pre-exposure prophylaxis by HCWs is not associated with a statistically significant reduction in risk of SARS-CoV-2. Most of the HCWs who took PrEPdid not experience any serious adverse side effect. The reasons behind non-acceptance/avoidance of the PrEP by HCWs were myriad but most commonly the surveyed HCWs refrained from providing any tangible reason.Recently the availability of vaccines has lowered the importance of chemoprophylaxis strategies, but having an effective chemoprophylaxis regimen vis-à-vis vaccine might be required in future as our knowledge regarding the exact pathophysiology of COVID-19 is still in a nascent stage.

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