

A SURVEY REGARDING PROPHYLACTIC USE OF HYDROXYCHLOROQUINE / CHLOROQUINE FOR COVID-19 AMONG HEALTHCARE WORKERS OF PAKISTAN

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ABSTRACT

Objective: To ascertain the trend of healthcare workers of Pakistan towards prophylactic use of Hydroxychloroquine/Chloroquine.

Study Design: Cross-sectional study.

Place and Duration of Study: Rawalpindi Institute of Cardiology, Rawalpindi, from May 2020 to Jun 2020.

Methodology: The online survey included Health care workers of Prominent Medical Institutes of Pakistan which were selected using non-probability consecutive sampling technique. The respondent's identity was kept anonymous. All Healthcare workers, asymptomatic at the time of study were included. Those who were already COVID-19 positive, had any symptoms of COVID-19 or were hospitalized because of any illness were excluded from the study.

Results: Data collected from 500 Healthcare workers showed that 130 (26%) of them used Hydroxychloroquine /Chloroquine for prophylaxis. Hydroxychloroquine was consumed by 119 (91.5%), and Chloroquine by only 11 (8.5%). Furthermore, 61 (47%) used the medication only once, while 46 (35.38%) took stat doses and once weekly. The rest, 15 (11.5%), and 8 (6.1%) took medication at 3 weeks and 2 weeks intervals after stat doses respectively. Out of 130 Healthcare workers, 43 (33.1%) were still using the medication one week, two weeks, and three weeks apart.

Conclusion: In order to establish the prophylactic role of Hydroxychloroquine /Chloroquine effectiveness against COVID-19, clinical trials are direly needed and in the meantime Healthcare Workers of Pakistan need to keep in mind the lack of data regarding the efficacy of these drugs as prophylactic agents and also the potential safety concerns with their use.

Keywords: Chloroquine, Chemoprophylaxis, COVID-19, Hydroxychloroquine.

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INTRODUCTION

More than 200 million people stand at the escarp of a surge in recent COVID-19 cases in Pakistan as the disease reaches pandemic proportions with substantial morbidity and mortality. It is estimated that the number of COVID-19 patients in Pakistan is significantly more than reported due to lack of adequate tests being conducted¹. Healthcare workers are amongst the most vulnerable groups being exposed to the disease on daily basis. Infected Healthcare workers in their asymptomatic period pose a serious threat to their contacts including COVID

unrelated patients². For these reasons preventive strategies for those exposed were sought out all over the world such as pre-exposure or post-exposure prophylaxis³.

Some Studies conducted in China suggested marked efficacy of chloroquine phosphate as a therapeutic agent in COVID-19⁴⁻⁶. This led the Chinese experts to recommend that patients with COVID-19 should be treated with chloroquine⁷. Advocates around the world, including the President of United states began to substantiate the safety and efficacy of Hydroxychloroquine, the drug which got an emergency permit from United States Food and Drug Administration as well as International Medical Councils⁸. However no studies as of yet have been conducted that ascertain the use of Hydroxychloroquine (HCQ)

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Received: 29 Jun 2020; revised received: 27 Jul 2020; accepted: 27 Jul 2020

/Chloroquine (CHL) as an effective prophylactic agent for this disease.

Regardless of an absence of a peer-reviewed publication that justifies the use of HCQ/CHL as potent prophylactic agents against the virus, clinicians worldwide adopted multiple prophylactic regimens. Despite the uncertainty of these drugs efficacy, the global panic led many medical and scientific bodies around the world to endorse the chemoprophylaxis with HCQ/CHL⁹. The overly optimistic perception among the Healthcare workers disregarded the risk-benefit assessment resulting in widespread self-medication.

Our study aimed to conduct a survey in Pakistan, among the Health care workers regarding their trend towards the prophylactic use of HCQ/ CHL.

METHODOLOGY

A cross-sectional survey was conducted among the health care workers (HCW) of Pakistan at Rawalpindi Institute of Cardiology, from 1st May 2020 to 1st June 2020. The HCWs were selected using non-probability consecutive sampling technique. The identity of the respondents was kept anonymous. All those HCWs who were currently working in different tertiary care hospitals of Pakistan who were willing to respond to the questionnaire were included in the study. Those who had current respiratory symptoms, recent hospitalization because of any illness or not willing to fill the questionnaire were excluded from the study. Based upon a similar study conducted previously¹⁰, a minimum sample of 250 respondents was calculated using the WHO sample size calculator. Responses were sought from HCWs to ascertain the percentage of those who had used or were currently using Hydroxychloroquine/Chloroquine as a prophylactic drug, and have advised others regarding its utilization. It was also explored in the survey, what factors influenced them to use HCQ/CHL and which regimen did they adopt. Approval was taken from Ethical Review Committee (RIC/RERC 15/20) on 11/7/20.

Categoric variables are expressed as percentages. All statistical analyses were performed with SPSS (SPSS Inc. Chicago, IL).

RESULTS

Data collected from 500 Healthcare workers, comprising Physicians 365, (73%), Nursing 114 (22.8%) and Para medical Staff 21 (4.2%) showed that 130 (26%) of them used Hydroxychloroquine /Chloroquine for prophylaxis. Majority of the Healthcare workers who used the medication were Physicians as shown in fig-1.

Out of all, who used the medication, 97 (75%) prescribed/ advised the medication to their

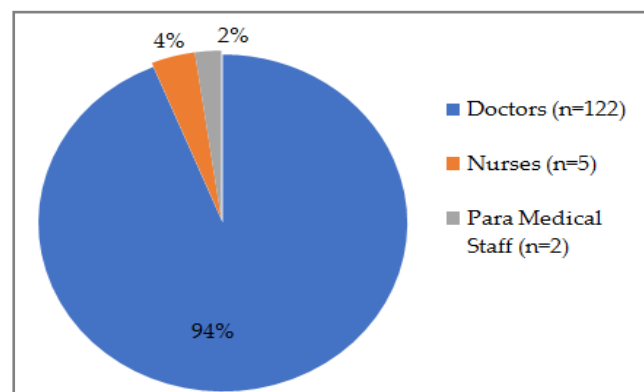


Figure-1: Distribution of HCWs who used HCQ/CHL for prophylaxis of COVID-19 in Pakistan.

friends and families.

Lacking a standardized chemo-prophylactic regimen, multiple dosage schedules were adopted by the HCWs of Pakistan.

119 (91.5%) of the Healthcare workers preferred Hydroxychloroquine over Chloroquine, the latter was used by only 11 (8.5%) of them.

Furthermore, 61 (47%) used the medication only once, while 46 (35.38%) took stat doses and continued taking once weekly. The rest, 15 (11.5%), and 8 (6.1%) took medication at 3 weeks and 2 weeks apart after stat doses (200/400/800 mg for HCQ and 150,250,500 mg for CHL) respectively as shown fig-2.

It was observed by our survey that out of 130 Healthcare workers, 43 (33.1%) of them were still using the medication one week, two weeks, or three weeks apart.

We also found out that 69 (53%) Healthcare workers using the medication were influenced by the Medical Literature, while a significant 39 (30%) number followed their friends and colleagues and took the medicine as a prophylactic measure as represented by the graph fig-3.

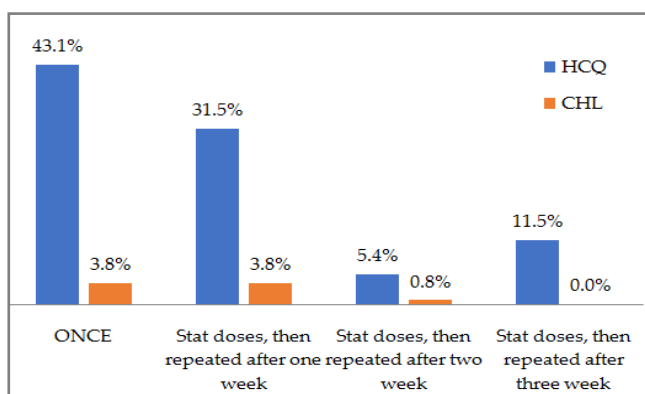


Figure 2: Percentages of Dose Regimen adopted by the HCWs.

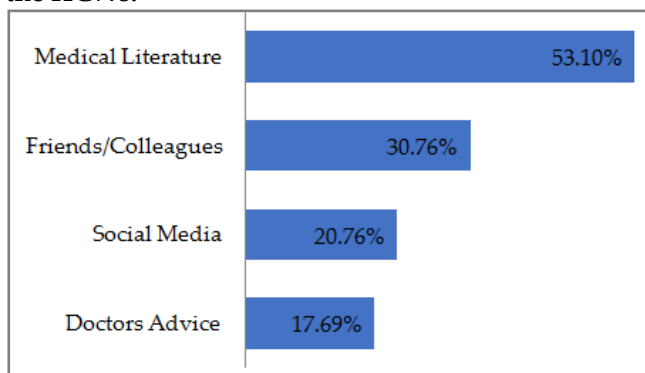


Figure-3: Factors that Influenced the HCWs to use HCQ/CHL as prophylaxis.

DISCUSSION

The recent Health crisis due to SARS-COV-2 infection, with no yet available specific treatment, pushed the world in a frantic search for a cure as the morbidity and mortality, associated with the virus, spiked substantially in various parts of the world. Some studies claimed that CHL has shown in vitro antiviral activity against SARS-CoV-2 due to its ability to inhibit the entry pathways of the virus thus hampering the viral replication, and theorized that the same activity in vivo could help in treatment¹¹. It was also suggested that in COVID patients, if early

treatment with these medication is initiated, it could help prevent the possible progression of the disease to a critical state, even HCQ was recommended to be used in critical patients instead of corticosteroids and Immunomodulators¹¹. In contrast, some previous, in vivo studies conducted to observe HCQ/Chloroquine effect on viruses such as influenza, dengue, and chikungunya showed that rather than slowing down the viral replication, it enhances it and consequently increases disease severity. Indicated by some clinical trials, chloroquine treatment was inadequate to prevent influenza and chikungunya virus infection. It was suggested that their use may escalate the risk of infection as well as symptoms severity^{12,15}.

Both these drugs portray anti-inflammatory activity, owing to which they are being used to treat Systemic lupus erythematosus, Rheumatoid Arthritis and Osteoarthritis¹³. So it was speculated that this anti-inflammatory and immunomodulatory activity may prove beneficial against COVID induced acute lung inflammation. As the pandemic worsened, HCWs around the world lacked the effective therapy to overcome the viral disease, initial studies related to the promising role of CHL/HCQ that originated in China led the researchers around the globe to indulge themselves ratifying the efficacy of these drugs¹⁴.

Clinical trials which were conducted in China apparently depicted sufficient efficacy and safety of CHL in treatment of COVID-19^{4,6}. The data those trials represented had some inaccuracies later expressed in FASEB journal which casted doubts on results of those trials¹⁴. Still, the Chinese experts recommended that all COVID patients who do not have any contraindication to the drug or those having renal or hepatic disease should be treated with a dose of 500 mg chloroquine twice per day for 10 days⁷.

Many hypotheses were drawn based on the fact that, due to large volume of distribution of HCQ in liver, kidneys, lungs and other organs, HCQ may inhibit viral replication in the tissues if effective concentrations are achieved. One

study suggested dosing regimen for treatment of COVID-19 using PBPK (Physiologically based pharmacokinetic modeling) models, but no evidence from human trials was actually depicted. The model however illustrated higher potency of HCQ as compared with CHL in subsiding a cytokine storm that occurs in COVID-19¹¹.

A French study also claimed that HCQ was effective in viral clearance in patients when compared with control group. However, due to its flawed methodology it received wide criticism. A statement was later issued by the publishing authority accepting the inadequacies¹⁴.

Many controversial and disputed studies followed and were rendered inadequate considering their limitations and scarce data¹⁴.

Clinical trials were under process, being conducted on numerous antiviral drugs, yet no specific pharmacological treatment that had proven to be effective was made available. HCQ and chloroquine were hesitantly included among other drugs for treatment of COVID-19 in context of a clinical trial^{3,9}. Despite the uncertainty of these drugs efficacy, the global panic led many medical and scientific bodies around the world to endorse chemoprophylaxis with HCQ/CHL, speculating the possible dosing regimen with CHL as initial dose of 300 mg followed by 100 mg daily intake^{8,9}.

As Healthcare workers are amongst the most vulnerable groups being exposed to the disease on daily basis, 2 preventive strategies for those exposed were being sought out all over the world such as pre-exposure or post-exposure prophylaxis³. Even in the absence of a peer-reviewed publication that justifies the use of HCQ/CHL as potent prophylactic agents against the virus, clinicians worldwide continued adopting HCQ/CHL in multiple prophylactic regimens.

The overly optimistic perception among the Healthcare workers regarding the use of HCQ/CHL as prophylactic agents disregarded the risk-benefit assessment and resulted in widespread self-medication.

Recent Studies published in FASEB has warned the use of HCQ/CHL for treatment of COVID patients as the immunologic actions of these drugs could result in significant unwanted adverse effects in COVID patients by causing antigen presentation suppression as well as production of cytokines. These drugs may prove to be detrimental to the innate and adaptive immune responses. It was also recommended that the use of these drugs should only be limited to a clinical trial¹⁴.

Chloroquine has been previously associated with an increased incident of infections with Human Immunodeficiency Virus, Herpes zoster infections and expression of Epstein-Barr virus in regions where it was prescribed for malaria, as it was observed to have increased the virulence of the viruses by interfering with the production of endogenous interferon¹⁵.

There is insufficient data available to ascertain whether HCQ/CHL has any role in either the treatment or prophylaxis and It was observed in our survey that out of 500, randomly selected HCWs throughout Pakistan, 130 used the medication and prescribed to friends and family as a prophylactic agent. Most of them were influenced by the Published Medical Literature, which as debated earlier had been controversial when it comes to proving the efficacy of these drugs. No conclusive dosing regimen has been accepted as of yet with respect to both Chloroquine and hydroxychloroquine, however it is evident from our survey that HCWs were following multiple schedules on their own. There are increasing concerns about the safety of these drugs as both medications have been associated with serious life threatening adverse reaction¹⁶. Prophylactic use at a broad scale may expose the population to such adverse reactions that include arrhythmia, sudden cardiac death, and fulminant hepatic failure^{16,17}. Many medicines have been withdrawn because of adverse reactions after showing initial clinical promise.

One study that focused on post-exposure prophylaxis of COVID-19 reported that there was

no added advantage of HCQ being used as a prophylactic agent. Although there were some limitations to that study, the researchers included such participants who had close contact with a confirmed COVID-19 patient and were administered either HCQ or a placebo as post-exposure prophylaxis. The results, however, were not statistically significant¹⁸.

It was observed that in hospitalized COVID patients, HCQ had no association with either a substantial higher or lower risk of mortality, however the study conducted on these patients claimed that due to certain limitations in their approach the result should not be interpreted to define absolute inadequacy of HCQ treatment¹⁹.

Hence, clinicians should exercise caution, before using HCQ/CHL, as despite the proven in vitro efficacy, there is no authentic publication of clinical trial results and there is a need to understand COVID-19 pathogenesis further²⁰.

Many speculations have been drawn regarding the possible prophylactic role of CHL/HCQ owing paradoxical published studies. However none of the studies have actually provided any conclusive evidence. The ongoing Pandemic may lead the masses to self-administer these drugs in quantities not yet approved or recommended for either prophylaxis or treatment. This will ultimately increase the risk of every individual taking the drug to its potential harmful effects as described earlier. Therefore HCWs have the responsibility to make recommendations based on clinical evidence rather than indulging themselves in speculations. The Hippocratic Oath of "First Do no Harm" should guide HCWs to take decisions, keeping in mind the risk-benefit ratio of administration of CHL/HCQ²¹.

The inappropriate interpretation of the literature by public leaders has the potential to do serious harm. For these reasons, it is strongly recommended that patients should only be using these drugs as a treatment or as prophylactic measure in context of a clinical trial.

CONCLUSION

The survey conducted shows that HCWs of Pakistan did indeed use the medication and also prescribed it to others as a preventive measure despite of no evidence as an effective prophylactic agent. In order to establish the prophylactic role of HCQ/CHL effectiveness against COVID-19, clinical trials are direly needed and in the meantime HCWs of Pakistan need to keep in mind the lack of data regarding the efficacy of these drugs as a prophylactic agent and also the potential safety concerns with their use.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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