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HyPE study: hydroxychloroquine prophylaxis-related adverse events' analysis among healthcare workers during COVID-19 pandemic: a rising public health concern

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ABSTRACT

Background The rising burden of Coronavirus disease (COVID-19) has led to the mass use of hydroxychloroquine by healthcare workers (HCWs). Adverse event profile of this drug when used as prophylaxis is not well known in the literature.

Methods A retrospective, cross-sectional study was conducted across the country using semi-structured web-based questionnaire among COVID-19 negative and asymptomatic healthcare workers, taking hydroxychloroquine prophylaxis. Descriptive and multivariate logistic-regression models were applied for analysis.

Results Of the 166 participants, at least one adverse event was experienced by 37.9% participants, gastrointestinal being the most common (30.7%). Risk was higher in participants <40 years age (odd's ratio (OR): 2.44, 95% confidence interval (CI): 1.18–5.05) and after first dose of hydroxychloroquine (51.2%, OR: 2.38, 95%CI: 1.17–4.84). Hydroxychloroquine prophylaxis was initiated without electrocardiography by 80.1% of HCWs. Only 21.6% of those with cardiovascular disease could get prior ECG.

Conclusions A higher incidence of adverse events was observed when results were compared with studies involving patients on long-term hydroxychloroquine therapy. Younger age and first dose were associated with greater incidence of adverse events though all were self-limiting. Monitoring prior and during prophylaxis was inadequate even among those with cardiovascular disease and risk-factors. However, no serious cardiovascular events were reported.

Keywords adverse effects, COVID-19, hydroxychloroquine, prophylaxis

Introduction

COVID-19 caused by Severe Acute Respiratory Syndrome–Coronavirus 2 (SARS-CoV-2) was officially declared as pandemic on 11th March 2020 by World Health Organisation. Among the many unprecedented challenges thrown by COVID-19, protecting healthcare workers was one of them. Infection rate among healthcare workers managing COVID-19 patients has been estimated to vary from 4.4% in China[1] to 20% in Italy.[2] An age old drug, Chloroquine, with proven efficacy against several viral diseases,[3] and its congener

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hydroxychloroquine, having attained success in *in vitro* studies on SARS-CoV-2,[4] shot into the limelight as a modality of treatment as well as prophylaxis.[5,6] Given its safety track record,[7] National Task Force Implemented by Indian Council of Medical Research (ICMR)[8] put forth the recommendation for hydroxychloroquine as prophylaxis of healthcare workers. Even though the use of hydroxychloroquine has been known for a plethora of conditions, mass use of the drug by an apparently asymptomatic population was not known prior to the advent of this pandemic. Owing to a dearth of studies on the safety profile of this drug when used out of the usual known indications, and lack of evidence-based data in this setting, this study was conducted.

Background

Hydroxychloroquine—history, hoax and hope

The one among very few 'rays of hope' (see Fig. 1) in 2020, when world is trying to fight back COVID-19, has a history which dates 350 years back, when in 1638, a patient from Peru's Viceroy's family, countess cinchona, contracted Malaria.[9] She was cured with bark of a tree called Jesuit's bark. It took 200 years to isolate its active ingredient 'quinine'. In 1945, quinine was hydroxylated to form hydroxychloroquine, a safer derivative. The drug has continued its glorious march since then. Currently, the drug is United States Food and Drug Administration (FDA) approved for Malaria, discoid lupus erythematosus, systemic lupus erythematosus (SLE) and rheumatoid arthritis.

Hydroxychloroquine sulfate (blood half-life 537 hours or 22.4 days) attains peak blood levels 3.26 hours after administration of 200 mg salt (155-mg base) orally in healthy males.[10] Absorption of the drug was found to be less in patients with rheumatoid arthritis with severe disease activity compared with the less severe groups. This observation may have significant importance while ascertaining dosage recommendation in healthy subset of population.

Hydroxychloroquine and COVID-19

Yao *et al.*[11] showed *in vitro* effect of hydroxychloroquine on SARS-CoV-2 infected vero-cells using physiologically based pharmacokinetic models. Liu *et al.*[12] in the *in vitro* study on vero-cells showed inhibitory effect of hydroxychloroquine on entry and post-entry steps of viral replication. Open label non-randomized trial showed the reduction of viral carriage in 20 patients after administering hydroxychloroquine.[13] A Randomized Control Trial conducted in Wuhan, China showed improvement in 25 out of 31 patients in the treated group.[14] In view of the favourable outcomes and desperate situation born out of this pandemic, the FDA under Emergency Use Authorization recommended the use of this drug at doses of 800 mg on the first day and then 400 mg daily for 4–7 days based on clinical evaluation. However, optimum dose and duration of therapy remain unknown.[15] Various trials are underway on pre-exposure prophylaxis (see Supplementary data).

Need for this study

Previous prospective studies assessing side-effect profile of hydroxychloroquine are based on symptomatic patients taking the drug for various rheumatological conditions. Adverse effect profile of the drug on healthy asymptomatic population is lacking. Its importance is even more pertinent in view of its potential interaction with azithromycin, which also is known for QT prolongation. Potential risks associated with combining the drug with indigenous medicine with unknown content and tampering with recommended dosages was another grey zone, to which the study was directed at. With more number of people in general population, starting to consume the drug out of panic, un-scrutinized,[16] a study shedding light on the safety profile of the drug in asymptomatic population was a need of the hour.

Methods

Study design and setting

This was a cross-sectional study which ventured its journey from a dedicated COVID-19 Hospital in Bangalore, Bowring and Lady Curzon Hospital, Bangalore, Karnataka, India. It was conducted among healthcare workers involved in COVID-19-related services in various hospitals across India using web-based questionnaire.

Study population

'Direct contact groups' was designed to include healthcare workers involved in direct patient contact irrespective of personal protective equipment. This group included personnel involved in clinical services at out-patient department, designated COVID wards, screening block, Flu clinic and ICU. India, as on 22nd April 2020, the date of commencement of the study was at the stage of 'cluster of cases' as per WHO situation report −93; hence, those workers were included in direct group.[17] 'Indirect contact group' was meant for participants working in hospitals but not in direct contact with patients, which included administrative officials and COVID control room in-charges. 'No contact group' included non-hospital/non-clinic-based healthcare workers not directly involved in patient care.

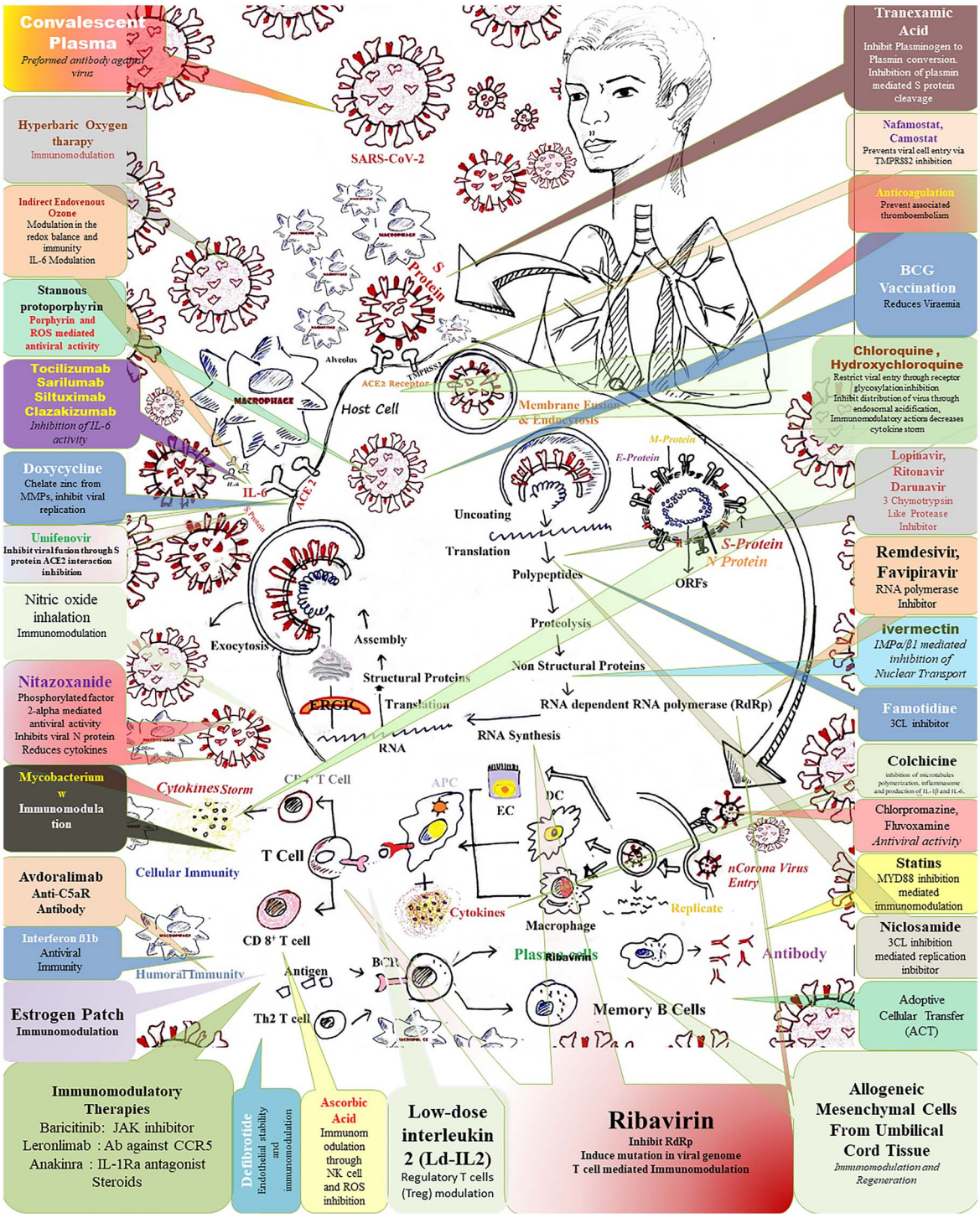

Fig. 1 Depicting proposed mechanism of transmission, viral replication cycle, pathogenesis and therapeutic options with proposed mechanisms for SARS-CoV-2. All drugs are investigational, ongoing trial results awaited.[18]

Participants were eligible for inclusion if they were health-care workers involved in COVID-19-related services, have taken at least one dose of hydroxychloroquine and were either negative for COVID-19 rt-PCR test or not tested. Participants were excluded from the study if they tested positive for COVID-19 rt-PCR, report of COVID-19 test was awaited, if they had symptoms of pre-existing disease in the last 4 weeks prior to the first dose of hydroxychloroquine or in case of

any recent change in dose of chronic medications or addition of new medications. The first two criteria ensured that only proven COVID negative cases were included in the study. The last two criteria of exclusion were meant to eliminate the confounding effect of symptomatic co-existing diseases and the effect of dose alteration of previous medications and counter the side-effects of a newly added drug on the adverse event profile of hydroxychloroquine.

Data collection

A web-based semi-structured questionnaire containing open- and close-ended questions with consent form was prepared on Google-forms platform. It was based on demographic parameters, pre-existing co-morbidities, any symptoms of pre-existing disease experienced by the patient over a period of 4 weeks prior to first dose hydroxychloroquine therapy, type of services with which each participant is involved, COVID-19 status, the duration of hydroxychloroquine intake, any modification in the dose outside the ICMR recommendation, use of any additional medications including non-allopathy, prior or subsequent ECG with findings and side-effect profile. Further details of the questionnaire are provided in the Supplementary data. The questionnaire was circulated among large doctors' and nursing social network forums across the country. This ensured that every member of the group had equal chance of getting included in the study. The questionnaire was circulated over a period of 6 days from 22nd April to 27th April 2020, which yielded a total of 174 responses. The questionnaire was restricted to single response from each participant.

Outcomes

The outcomes evaluated were the adverse event profile, practice and precautionary measures taken prior to and during hydroxychloroquine therapy.

Statistical analysis

The responses obtained were tabulated in spreadsheet, where first phase analysis was completed by measuring the frequency with percentage among categorical variables and mean ± standard deviation among continuous variable. This phase comprised the descriptive component of our study. The tabulated data were transferred to SPSS where second phase analysis was carried out using independent chi-square tests, to check for significance between independent and dependent variables with 95% confidence intervals (CIs). The dependent variable in our study was side-effect expressed as a dichotomous variable based on whether it was present or absent. Independent variable groups included sex, age group, cumulative dose of hydroxychloroquine, first dose effect (defined as cumulative dose <1gm), pre-existing co-morbidities and type of contact. In the third phase, a multivariate binomial logistic regression analysis model was applied to determine the effects of the above ascertained independent variables. Finally, odd's ratio (OR) and 95% CIs were calculated and the results were plotted on Forrest plot. For all analyses, SPSS, version 23 (IBM), and MS Excel were utilized.

Results

Participants and demographics

Out of 174 responses received, 8 were excluded based on exclusion criteria. The demographics of the study participants ($n = 166$), as described in Table 1, showed a predominant male distribution 122 (73.5%). Mean age of the study population was 36.3 (±11.8) years with 72 (43.4%) of the participants belonging to the age group of 26–30 years. About 164 (98.8%) of the respondents were doctors. About 132 (79.5%) of the participants were not tested for COVID-19, while 34 (20.5%) participants were tested negative for COVID-19 rt-PCR. Among the study participants, 111 (66.9%), 33 (29.7%) and 22 (3.4%) belonged to direct, indirect and no contact groups, respectively. Co-morbidities included hypertension 21 (12.6%), ischemic heart disease 2 (1.2%), diabetes mellitus 13 (7.8%), hypothyroidism 11 (6.6%), respiratory diseases 17 (10.2.1%), dyslipidemia 4 (2.4%), dermatological 7 (4.2%), gastrointestinal 1 (0.6%), musculoskeletal 1 (0.6%) and allergic disorders 23 (13.8%). The medication profile is detailed in Table 1. Family history of cardiac disease was present in 55 (33.1%) of the participants, which included atherosclerotic disease 45 (27.1%) and congenital heart disease 2 (1.8%). As far as chronic habits were concerned, alcoholism was the most prevalent 36 (21.6%) followed by smoking 15 (9.0%) and other substance use 3 (1.8%).

Excluded cases

Out of 174 responses, 8 were excluded. Details of them are mentioned in Supplementary data.

Practice of prophylaxis therapy

Out of 166 healthcare workers, self-modification of dose was done by 10 (6.0%) as mentioned in Supplementary data. Other prophylaxis practices was followed by 10 (6.0%) responders, out of which 7 (4.2%) took azithromycin as add-on and 3 (1.8%) took non-allopathy medications. About 133 (80.1%) of the participants initiated prophylaxis without prior ECG, while among those with pre-existing cardiovascular disease

Table 1 Demographics, clinical characteristics and adverse event profile of the study participants

Demographics—no. (%)	*All participants (n = 166) (%)*
Mean age (±SD)—years	36.3 (±11.8)
Median age	29.9
Sex	
Male	122 (73.5)
Female	44 (26.5)
Health care worker category	
Doctor	164 (98.8)
Others[a]	02 (1.2)
Contact pattern	
Direct	111 (66.9)
Indirect[b]	33 (29.7)
No contact	22 (3.4)
COVID-19 testing status[c]	
Tested negative	34 (20.5)
Not tested	132 (79.5)
Coexisting chronic Disease [d]	
Cardiovascular	
Hypertension	21 (12.6)
Ischemic heart disease	2 (1.2)
Diabetes	13 (7.8)
Respiratory[e]	17 (10.2)
Hypothyroidism	11 (6.6)
Dyslipidemia	4 (2.4)
Dermatological[f]	7 (4.2)
Gastrointestinal[g]	1 (0.6)
Musculoskeletal[h]	1 (0.6)
Allergic disorders[i]	23 (13.8)
Family history of cardiovascular disease	55 (33.1)
Atherosclerotic heart disease	45 (27.1)
Congenital heart disease[l]	2 (1.2)
Hypertension	8 (4.8)
Medication use	
Cardiovascular drugs	
Angiotensin system blockers	12
Beta blockers	4
Antihypertensive [j]	21
Statins	6
Metabolism and endocrine system drugs	
Antidiabetics	12
Thyroxine	10
Drugs of respiratory system	9
Beta agonist	4
Inhaled corticosteroids	3
Antihistaminics	2
Others[k]	4
Chronic habits	
Smoking	15 (9.0)
Alcohol use	36 (21.6)
Other substance use	3 (1.8)

(Continued)

Table 1 Continued.

Demographics—no. (%)	*All participants (n = 166) (%)*
Practice of hydroxychloroquine prophylaxis	
Prior ECG	33 (19.9)
Prior ECG among participants with cardiovascular disease or cardiovascular risk factors[m]	11 (21.6)[n]
Prior ECG in participants with hypothyroidism[o]	2 (1.2)
Dosing	
Participants following dosage as per ICMR guidelines[p]	156 (94.0)
Modified dosage	10 (6.0)
Other prophylaxis practices	10 (6.0)
Azithromycin as add-on therapy	7 (4.2)
Non-allopathy medications	3 (1.8)
Duration of prophylaxis taken	
1st week	43 (25.9)
2nd week	20 (12.0)
3rd week	50 (30.1)
4th week	38 (22.9)
≥5th week	15 (9.0)
Cumulative dose	
<1gm	43 (25.9)
1–2 gm	108 (65.1)
>2 gm	15 (9.0)
Monitoring of therapy	
ECG	21(12.6)
Any ECG changes	No changes reported

[a]Others include nursing staffs.

[b]Indirect contact group included participants working in hospitals but not in contact with patients. Respondents included district task force member, COVID control room workers, technical staffs and administrative personnel.

[c]COVID-19 positive status was an exclusion criterion.

[d]Some of the participants had more than one systemic pre-existing diseases, hence percentage not calculated.

[e]Respiratory diseases included both upper and lower respiratory tract chronic disease—allergic rhinitis, allergic rhinosinusitis, chronic bronchitis and asthma.

[f]Dermatological diseases included one case of lichen planus, focal psoriasis, urticarial vasculitis, eczema, allergic dermatitis, vitiligo and fungal dermatoses.

[g]Gastrointestinal disease included Irritable Bowel Syndrome.

[h]Musculoskeletal disease included one participant with arthritis—non-specified.

[i]Allergic disorder included dust allergy, pollen allergy, allergy to nitroimidazole and quinolones, bronchial asthma, allergic rhinitis, bronchitis and allergic dermatitis. Hence, this subgroup is having overlap with other systemic diseases.

[j]Antihypertensives were not specified by some of the respondents. Commonly mentioned were angiotensin system blockers, beta-blockers and calcium-channel blockers. Hence, percentage of the cardiovascular drugs mentioned in the table may be the same or higher.

[k]One participant was methotrexate (for focal psoriasis), one on dapsone (for urticarial vasculitis), one of mebeverine (for Irritable Bowel Syndrome) and one on itraconazole (for fungal dermatosis).

[l]One participant had family history of hypertrophic obstructive cardiomyopathy.

[m]Cardiovascular risk factors include hypertension, diabetes, dyslipidemia and hypothyroidism.

[n]Denominator was taken as the number of participants with pre-existing cardiac disease or cardiovascular risk factor (51 participants = 21 cardiovascular disease, 13 diabetes mellitus, 11 hypothyroid, dyslipidemia 4).

[o]Hypothyroidism is a proven risk factor for QT prolongation.

[p]Indian Council for Medical Research (ICMR) guidelines: hydroxychloroquine 400 mg twice daily on Day 1 followed by 400 mg weekly for 7 weeks as prophylaxis for healthcare personnel.[7]

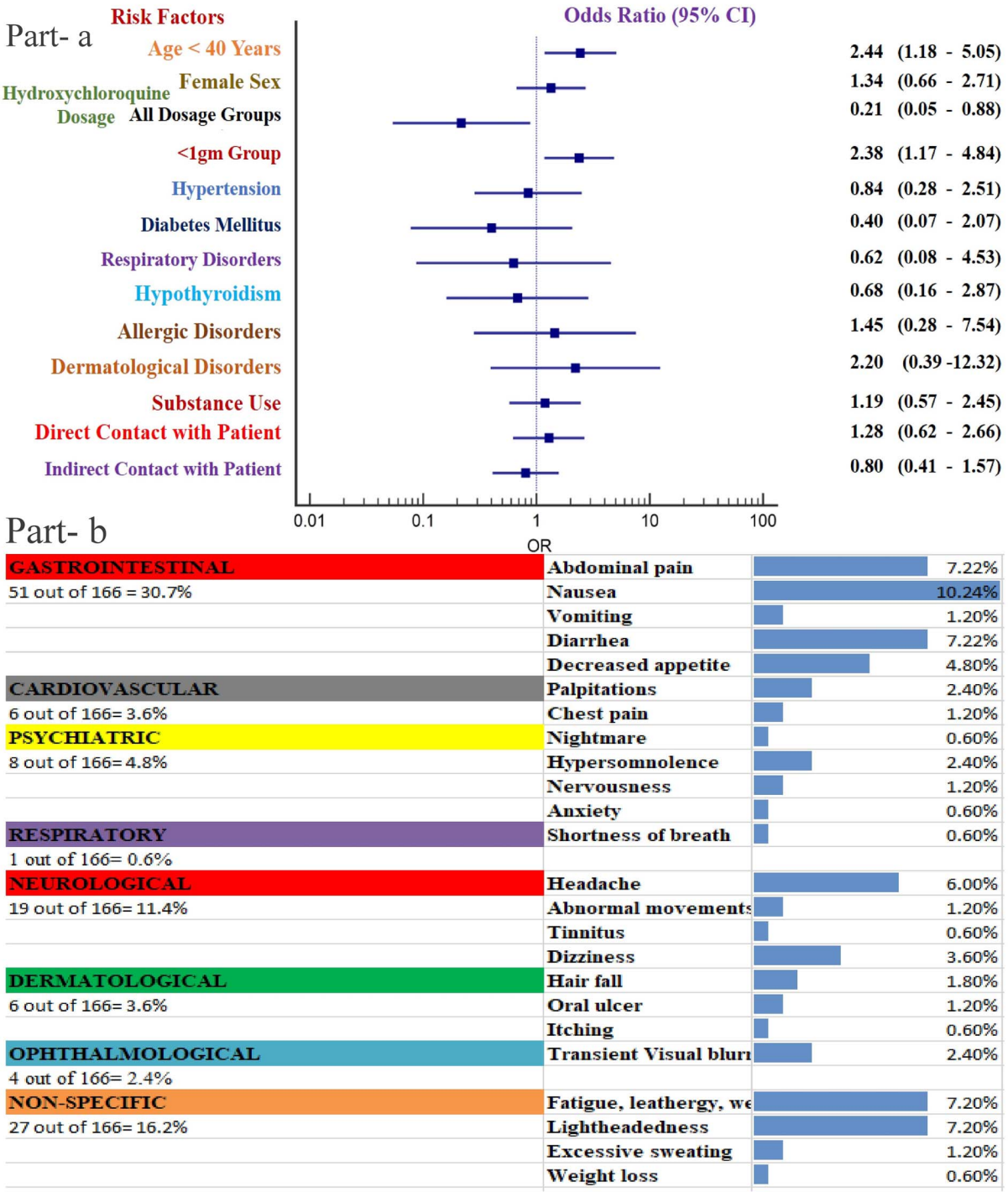

Fig. 2 (a) Showing odd's ratio and 95% CI plotted on logarithmic scale, of the risk factors predicting risk of adverse drug reaction with hydroxychloroquine prophylactic therapy. (b) Adverse event analysis based on the percentage of occurrence.

and/or risk-factor, prior ECG was present among 11 (21.6%) of them. Prior ECG among hypothyroid participants was done by 2 (1.2%) of the responders. Follow-up ECG was done by 21 (12.6%) of the total participants, and none of them had any ECG changes.

Adverse drug reaction

The side-effect profile analysis (Fig. 2, Table S1 in Supplementary data) highlighted that 63 (37.9%) of participating healthcare professionals experienced at least one adverse drug reaction following use of the drug. A number of

participants experienced more than one systemic side-effects. Among them, gastrointestinal effects had the maximum incidence with 51 (30.7%) events of adverse drug reaction. This was followed by non-specific events 27 (16.2%), neurological effects 19 (11.4%), psychiatric 8 (4.8%), cardiovascular 6 (3.6%), dermatologic 6 (3.6%), ophthalmological 4 (2.4%) and respiratory 1 (0.6%). Further dissection revealed nausea 17 (10.2%), decreased appetite 8 (4.8%), diarrhea 12 (7.2%), abdominal pain 12 (7.2%) and vomiting 2 (1.2%) being the prevalent gastrointestinal symptoms. Neurological symptoms included headache 10 (6.0%), dizziness 6 (3.6%), abnormal movements with extra-pyramidal symptoms 2 (1.2%) and tinnitus 1 (1.2%). Cardiovascular symptoms included palpitations 6 (3.6%) and chest pain 2 (1.2%). It is noteworthy that out of four patients with palpitations, three of them had the symptoms with first dose of the drug. Shortness of breath was experienced in 1 (0.6%) of subjects. Ophthalmologic side-effects noted were transient visual blurring 4 (2.4%). Dermatologic side-effects seen were hair fall, oral ulcer and itching among 3 (1.8%), 2 (1.2%) and 1 (0.6%) of the participants, respectively. Incidentally, one of the patients with oral ulcer was on mebeverine for Irritable Bowel Syndrome. Psychiatric manifestations included hypersomnolence 4 (2.4%), nervousness 2 (1.2%), nightmare 1 (0.6%) and anxiety 1 (0.6%). Other non-specific side-effects noted were lightheadedness 12 (7.2%), fatigue/lethargy/weakness combined 12 (7.2%), excessive sweating 2 (1.2%) and weight loss 1 (0.6%). Among participants taking azithromycin as add-on, 2 (out of 7) had gastrointestinal and 1 had non-specific side-effect. None of them had any cardiovascular adverse event. Among non-allopathy users, 1 (out of 3) experienced diarrhea, hair-fall and abnormal movement.

First dose event analysis

Out of 43 participants who have completed first dose of therapy, i.e. at <1 gm of cumulative dose, 22 of them (51.2%) developed at least one side-effect. This happens to be a noteworthy observation since further analysis revealed that the frequency of side-effects dropped to 38.9% in participants (42 out of 108) at cumulative doses between 1 and 2 gm. Beyond 2 gm, the side-effect frequency reduced further to 13.3% (2 out of 15 participants). However, it is worth mentioning that participants only at first dose of therapy (cumulative dose <1gm) was considered in this group. Beyond first week of therapy, participants with side-effects were not included due to the likely possibility of errors in recalling the exact week at which they might have had their symptoms, leading to recall bias.

Analyses based on epidemiological variables

Analysis showed participants of direct contact group had relatively higher occurrences of side-effects (40.5%) when compared with indirect contact group (33.3%) and no contact group (27.2%). Out of 62 participants having one or more pre-existing disease 19 (30.6%) of them had at least one adverse event. Out of 47 participants on at least one chronic medication 11 (23.4%) of them had at least one adverse event.

Multivariate binomial logistic regression analysis

The results analysed from the multivariate binomial logistic regression analysis, as depicted in Fig. 2, revealed that younger age (<40 years) (OR: 2.44, 95% CI: 1.18–5.05) was an independent risk factor for the development of side-effects. First dose of hydroxychloroquine, defined by cumulative dose <1gm, was found to be associated with higher incidence of adverse events (OR: 2.38, 95% CI: 1.17–4.84): association of female sex (OR: 1.34, 95% CI: 0.66–2.71), substance use (OR: 1.19, 95% CI: 0.57–2.45), direct contact with patient (OR: 1.28, 95% CI: 0.65–2.66) with higher incidence of side-effects. Association of pre-existing diseases with side-effect profile could not be concluded due to smaller sample size and heterogeneity in study population.

Discussion

Main findings of the study

In our study, a relatively higher incidence of adverse effects was found. Younger age (less than 40 years) and first dose were associated with greater incidence of adverse events though all were self-limiting. Monitoring prior and during prophylaxis was inadequate even among those with cardiovascular disease and risk-factors.

What is already known on this topic

The safety profile of hydroxychloroquine was illustrated in a systematic review conducted in 2010 by Ruiz-Irastorza *et al.*[7] which concluded that the toxicity of the antimalarials in the management of SLE was mild, infrequent and reversible. There have been a number of cohort studies undertaken to evaluate the long-term toxicity of this drug, some of which are enlisted in Table 2. Wang *et al.*in 1999,[19] in a prospective cohort study on 156 SLE patients taking hydroxychloroquine, over mean duration of 6.9 years, found side-effects as a cause of discontinuation of therapy among 29% study subjects, most common being gastro-intestinal (7%). Morand *et al.* [21] in a retrospective study on 366 RA and 37 SLE patients on hydroxychloroquine over a period of 8 years revealed that the reason for shorter duration of continuation in the RA subgroup was not toxicity related to hydroxychloroquine but rather lesser treatment benefits in RA subgroup. In a prospective cohort study by Costedoat-Chalumeau *et al.* in 2007,[22] among patients on hydroxychloroquine for a mini-

Table 2 Previous studies analysing various adverse events of hydroxychloroquine/chloroquine in patients with connective tissue disorders

Study	*Population group*	*Duration of follow-up*	*Toxicity*
Morand *et al.* 1992	366 RA, 37 SLE	8 years	Dermatological 1 (3%),
Clark *et al.* 1993[20]	121 early RA	6 months	Mild side-effects, no discontinuation of therapy
Wang *et al.* 1999	224 SLE patients	6.9 years	Gastrointestinal (7%), myopathy (1.3%), headache (1.3%), retinal toxicity (0.6%), ototoxicity (0,6%), skin rash (0.6%)
Van Jaarsveld *et al.* 2000[23]	120 early RA on HCQ and 99% was on NSAIDs also	136 patient years	Number adverse effect 91. Patient with at least one adverse effect: 49%. First events occurred at 27 weeks (9–95 weeks)
Wozniacka *et al.* 2006	28 SLE	7 months	Increase in QTc before and after CQ treatment (363 versus 372 ms, $P = 0.09$)
Costedoat-Chalumeau *et al.* 2007	70 SLE	7.9 years	Minor heart conduction defect (4%)
HyPE study 2020	166 Healthcare workers as prophylaxis	1–8 weeks	Gastrointestinal (30.7%), non-specific (16.2%), neurological (11.4%), psychiatric (4.8%), dermatologic (3.6%), cardiovascular (3.6%), ophthalmic (2.4%), respiratory (0.6%)

RA: rheumatoid arthritis
SLE: systemic Lupus erythematosus
HCQ: hydroxychloroquine
NSAID: non-steroidal anti-inflammatory drugs
CQ: chloroquine

mum duration of 1 year, with no pre-existing cardiac condition, found no cardiac conduction defect, changes in PR or QT interval in the study population. In a study by Wozniacka *et al.* in 2006,[24] on 28 SLE patients on chloroquine monotherapy for a minimum duration of 7 months, showed a tendency to rise in QT interval, tachycardia but no incidence of any other arrhythmia or conduction defects. As far as ophthalmological side-effects were concerned, in a retrospective cohort study by Nuanpan Tangtavorn et al.in 2016,[25] out of 234 patients, risk of hydroxychloroquine-related retinopathy was present among 3.28% of patients who had received HCQ for 660–828 days, amounting to cumulative doses from 80 to 130 g and daily dose from 1.9 to 4.4 mg/kg/day.

What this study adds

In our study, a relatively higher incidence of side-effects was found in comparison with other studies which involved patients with connective tissue disorders, on prolonged hydroxychloroquine maintenance therapy. Even though the reason remains elusive, one can probably argue that the study subjects here were apparently asymptomatic, in contrary to the common scenario where patients with rheumatological conditions suffering from a myriad of distressing symptoms take this drug along with multiple others. This perhaps exerts a masking effect on the adverse effects caused by hydroxychloroquine *per se*. The symptomatic relief obtained from the therapeutic effect of the drug in such cases seems to outweigh the adverse symptoms caused by it in an overwhelming majority of cases. The other way to interpret the probable cause of this is the added component of panic engulfing a significant proportion of frontline personnel as they face the challenging task of managing patients, and at the same time, seeing fellow healthcare workers succumbing to the same disease they have been entrusted to treat. In addition, there is a confounding factor of a comparatively wider knowledge base about the drug, which probably enhances the interpretation of symptoms resulting in a broader array of adverse events. Whether this pandemic has unmasked, the already known knowledge attitude practice gap among physicians with regards to pharmacovigilance of

adverse drug reaction[26] remains a matter of argument. Higher frequency of first dose side-effect and greater occurrence in younger age group, when used among asymptomatic individuals, will perhaps be answered in the upcoming WHIP (Will Hydroxychloroquine impede or prevent COVID-19),[27] PATCH (Prevention And Treatment of COVID-19 With Hydroxychloroquine),[28] SHARP (Safety and efficacy of Hydroxychloroquine for At-Risk Population)[29] and other trials.

Limitations

Our study results require further validation with randomized trials and larger sample size with greater representation from non-doctor community.

Conclusion

A higher incidence of adverse events was observed when results were compared to studies involving patients on long-term hydroxychloroquine therapy. Younger age and first dose were associated with greater incidence of adverse events though all were self-limiting, with no serious cardiovascular events. In times of global health crises such as these, where conventional research process using pen and paper-based questionnaire can be the potential source of fomite borne transmission of SARS-CoV-2, utility of web-based study comes to the forefront as it enhances the reach of the study to a wider population base, over a shorter period of time.[30,31]

Supplementary data

Supplementary data are available at the *Journal of Public Health* online.

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