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A SURVEY ON ASSESSMENT OF ADVERSE EVENTS ASSOCIATED WITH HYDROXYCHLOROQUINE PROPHYLAXIS IN HEALTH CARE WORKERS

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Abstract

Background: There has been considerable debate regarding role of hydroxychloroquine (HCQ) as chemoprophylaxis against COVID-19 exposure in health care workers (HCWs). HCQ is being used since decades for treatment of malaria, rheumatoid arthritis and systemic lupus erythematosus, its reported side effects are mainly relevant to long term. For the chemoprophylaxis against COVID -19, the duration of administration of HCQ is limited to few weeks. The conclusive evidence for effectiveness of HCQ in COVID-19 is yet to come, meanwhile, the present study was conducted to evaluate its safety profile when used for prophylaxis in HCWs. **Methods:** The present study is a cross-sectional study conducted among the health care workers posted in COVID-19 intensive care units. The participants were telephonically interviewed and data including demographic parameters, details of chemoprophylaxis with HCQ and side effects experienced were collected.

Results: A total of 147 HCWs out of 197 acknowledged taking HCQ for prophylaxis against COVID-19. Forty participants reported experienced at least one adverse drug reaction following use of the drug. Among the adverse drug reactions gastrointestinal side effects were observed in 17.68% of participating HCWs followed by non-specific complains and skin problems and cardiovascular side effects. More side effects occurred in participants younger than 40 years, and those having co-morbidities. **Conclusion:** There incidence of adverse events when HCQ is used as prophylaxis against COVID-19 by HCWs is found to be 27.2%. The reported adverse events are predominantly self-limiting and younger age and presence of co-morbidities has been found to linked to increased risk of adverse events.

Keywords- hydroxychloroquine, prophylaxis, adverse events

Introduction

Health care workers (HCWs) are in the frontline against the ongoing Covid-19 pandemic and are particularly exposed to Covid-19 infection. According to many reports across the world, thousands of nurses and doctors contracted the virus since the onset of the Covid-19 pandemic[1-2]. The high rate of infection among HCWs is a serious concern as it causes depletion of workforce against the current global health crisis and also poses a risk of transmission of infection to colleagues, family members or patients suffering from other diseases or ailments.

Hydroxy-chloroquine is an antimalarial drug used widely since last 70 years. It has anti-inflammatory, immunomodulatory activity and has also proven efficacious against a large variety of viral infections. It has been suggested for chemoprophylaxis against exposure to Covid-19 infection in HCWs. More than 40 randomized clinical trials have been registered in less than 2 months from 13 different countries to evaluate the efficacy of HCQ for chemoprophylaxis[3].

A recent case-control study demonstrated that consumption of four or more maintenance doses of HCQ taken in combination with use of PPEs led to significant reduction in the odds of COVID-19 infections in the HCWs[4]. As the results of more studies evaluating the efficacy of HCQ for chemoprophylaxis is yet to come, we planned present study to specifically assess the associated side effects when HCQ used as chemoprophylaxis against COVID-19 infection in HCWs.

Methods

The present study is a retrospective cross-sectional study conducted among the health care workers posted in COVID-19 intensive care units in a tertiary care designated COVID hospital.

Study population

The study population consisted of health care workers involved in care of COVID-19 patients in ICUs. At the time of planning and conduct of study, no previous data on incidence of side effects of HCQ when it is used as

prophylaxis was available in literature. Hence a convenience sample of HCWs working in COVID-19 ICUs were taken for study.

Health care worker was defined as persons who were serving in healthcare setting and who has the potential for direct or indirect exposure to patients or their infectious secretions and materials (e.g. doctors, nurses, ICU technicians, housekeeping workers, nursing attendants, clinical trainees). The names and phone numbers of HCWs were obtained from the staff in-charges of ICUs. Participants were eligible for inclusion if they were HCWs involved in direct patient care and have taken at least one dose of hydroxychloroquine. Participants found taking any chronic medication/s were excluded if there was any recent alteration in medication/s dosage or any new drug was added to treatment.

Study Protocol

The study was conducted from 15April to 15 May 2020. The participants were interviewed telephonically by the designated study team members S.R. and K.S. Participation in survey was voluntary and no incentive was offered for this. For participation, verbal consent through telephone was obtained from eligible candidates. To minimise risk of transmission of SARS-CoV2 between participants and trial staff, written consent was not sought. All interviews were conducted in Hindi language. The interview questions were developed based on a literature review of relevant articles focusing on adverse events associated with use of HCQ and risk factors for occurrence of side-effects. After input from members of the departmental scientific committee, the survey was piloted among 30 health workers. Comments and suggestions received from pilot study were incorporated, and the revised questions were then reviewed by the investigators and a consensus was achieved before commencement of the study. The overall content validity index for questionnaire was 0.97. The questions had kappa value ranging from 0.41 to 0.94. The data obtained from participants utilized for pilot study was not included in analysis of main study.

Data Collection

The data collected included demographic parameters, job profile, pre-existing co-morbidities and drug intake history, any recent symptoms of pre-existing conditions, details of chemoprophylaxis with HCQ, duration of HCQ prophylaxis intake, any alteration from Indian Council of Medical Research (ICMR) recommendation in dose of HCQ[5], electrocardiogram findings (prior or after initiation of HCQ prophylaxis) and side effects experienced after intake of HCQ tablets.

Statistical analysis

The statistical software SPSS version 24.0 was used in the analysis. Statistical analysis was performed by using descriptive and inferential statistics with Pearson chi-square test. The categorical variables were expressed as frequency with percentage and continuous variables as mean ± standard deviation. P-value less than 0.05 was considered as significant at 95% confidence level.

Results

A total of 208 HCWs working in ICUs were identified; out of which 11 could not be contacted telephonically. Rest of 197 respondents gave verbal consent for participation in study and out of them 147 HCWs acknowledged intake of HCQ for chemoprophylaxis against COVID-19. The demographic characteristics of the participants are shown in table 1, which showed predominate male (59%) doctor (60.5%) distribution. The mean age of study population was 34. 49 ± 23 years with 78% of participants belonging to less than 40 years of age. Co-morbid conditions were identified in 19.7% (29/147) of participants. Co-morbidities included allergic disorders 7.4% (11/147), hypertension 6% (9/147), diabetes 2% (3/147), hypothyroidism 2% (3/147) and skin disorders 1.3% (2/147).

Dose of HCQ prophylaxis as per ICMR recommendation was followed by all participants except one. Prior to initiation of HCQ prophylaxis baseline electrocardiogram was done by only 12 HCWs. Majority of respondents (132/147) took HCQ for more than 5weeks in the cumulative dosage of more than 2 grams (133/147).

A total of 40 participants reported experienced at least one adverse drug reaction following use of the drug. Among the adverse drug reactions gastrointestinal (g.i.)side effects were observed in 17.68% of participating HCWs followed by non-specific complains and skin problems in 6% and cardiovascular side effects in 3.4%. The g.i. symptoms included diarrhoea, abdominal pain/discomfort, nausea, vomiting and oral ulcers (Table). Five respondents reported to experience palpitations with one of them subsequently demonstrated prolonged Q-T interval in ECG. One participant experienced exacerbation of psoriasis and one experienced palpitation with skin rashes. Non-specific complains commonly reported included headache, dizziness, malaise and lethargy. None of the participants had any ophthalmological, respiratory or psychiatric side effects.

Seven HCWs reported to stop HCQ after first dose; six of them experienced one or more of the side-effects. Two participants experienced palpitations, two reported headache, malaise and lethargy whereas exacerbation of psoriasis and oral ulcers were also reported by with first dose.

There was significant difference observed with occurrence of adverse drug reactions and age, job profile and presence or absence of co-morbidities in participants. More side effects occurred in participants with age less than 40 years (p=0.044), nursing staff (0.003) and those having co-morbidities(p=0.026). Side- effects are also significantly more observed with first dose of HCQ (p=0.00).

Table 1: Demographic characteristics of participants and the profile of hydroxychloroquine intake

Mean age	34.49
Less than 30 years	63
31-40 years	52
More than 40 years	32
Sex	
Male	87 (59.1%)
Female	60(40.81%)
Job Category	
Doctors	89(60.52%)
Nursing Staff	34 (23.12%)
Technicians	24(16.3%)
Co-existing conditions	
Allergic disorders (asthma, bronchitis, urticaria, sinusitis)	11
Hypertension	9
Diabetes	3
Hypothyroidism	3
Psoriasis	1
Vitiligo	1
Renal calculi	1
History of drug intake	
Antihypertensives Beta blockers Angiotensin receptor blocker	 6 7
Oral hypoglycemic(metformin)	1
Thyronorm	3
Corticosteroids Inhaled Systemic	 7 1
Antihistamincs	5
Dosing of HCQ for prophylaxis	
As per ICMR guidelines	146
Modified dosage	1
ECG done prior to initiation of HCQ prophylaxis	12
Duration & dose of HCQ prophylaxis taken	
1 week	7
2 weeks	3
3 weeks	1
4 weeks	4
More than 5 weeks	132
Cumulative dose of HCQ taken	
Less than 1 gm	7
1-2 gm	7
More than 2 gm	133

Table 2: Profile of Health Care workers (HCWs) experiencing adverse drug events

Number of HCWs reporting adverse drug events		40		
		Adverse drug events		P value
		No(n)	Yes(n)	
Age	<30 years	52	11	0.044
	31-40 years	36	16	
	>40 years	19	13	
Gender	Male	66	21	0.313
	Female	41	19	
Job category	Doctors	68	21	0.003
	Nursing staff	20	14	
	Others	19	5	
Co-morbid conditions	Yes	17	13	0.026
	No	90	27	

Table 3: Side -effects of hydroxychloroquine

Side effect (percentage of participants)		Number of participants experiencing side-effects
Gastrointentinal side effects (17.68%)	Diarrhoea	12
	Nausea & abdominal discomfort	2
	Gastritis	7
	Abdominal pain	3
	Vomiting	2
	Oral ulcer	1
Cardiovascular (3.40%)	Palpitations	5 (1 had prolonged QT interval in ECG)
Dermatological & Others (6.1%)	Exacerbation of psoriasis	1
	Palpitation and rash	1
	Headache	2
	Headache, dizziness and stomache	1
	Headache, vomiting	1
	Malaise, bodyache, lethargy	2
	Mild leg cramps	1
	Water retention, malaise	1

Discussion

Hydroxychlorquinone a 4-aminoquinolone, is derivative of chloroquine (CQ) having antimalarial, anti-inflammatory and immunomodulatory effects. It has been widely used as an antimalarial medicine and as treatment of SLE and RA for decades[6] .Based on in -vitro studies and experience of SARS 2003 outbreak, there is newfound interest in HCQ for treatment of COVID-19 patients and as prophylaxis for the close contacts[7,8] .However there are concerns and disputes about both safety and efficacy of HCQ over its these new applications in COVID -19 infection[9,10]. Hence the present study was conducted to evaluate the safety profile of HCQ when it is used as chemoprophylaxis in HCWs against COVID-19 infection.

The National Task Force for COVID-19 of ICMR in a bulletin dated March 21,2020 recommended the use of HCQ for prophylaxis in frontline asymptomatic HCWs caring for suspected or confirmed COVID-19 patients and household contacts of confirmed patients[5]. We excluded HCWs involved in indirect patient care (administrative staffs; not coming in direct contact of patients) in the present study. According to ICMR guideline and our institutional protocol; HCQ prophylaxis was suggested only for those HCW who are at high risk of contracting infection and hence we expected lower probability of HCQ intake by HCWs who were not in direct contact with COVID-19 patients. Participants were also excluded if there has been any recent alteration in their medication history (increase in dosage or addition of any new drug) so as to eliminate the confounding effect of medication alteration on side-effects of HCQ.

There is paucity of literature on the side effects of HCQ when it is utilized as a prophylactic agent. Most of the available data about adverse effect profile is related to therapeutic long-term use of HCQ. Ruiz-Irastorza in a systematic review of 95 articles involving SLE patients

using CQ and HCQ reported prevalence of side effects between 3 to 50% with preponderance of mild adverse events[11]. A recent retrospective study by Nagaraja et al found adverse effects to be reported by 37.9% of participants when HCQ is taken by HCWs for prophylaxis of COVID-19[12]. In our study population 27.2% of HCWs attributed at least one adverse effect to HCQ prophylaxis.

The adverse events of HCQ have been categorized into two; mild to moderate gastrointestinal and dermatological manifestations, and severe cardiovascular, ocular and neuromuscular manifestations. The most common reported adverse drug events of HCQ are gastrointestinal side effects. Previous studies have reported G.I. side effects to occur in 7 to 10 % of patients taking HCQ for SLE with average duration of use 6.9 years/patients[13,14]. In our study cohort the incidence of G.I. side effects was observed in 17.68% of participants. Frust et al reported gastrointestinal side-effects observed were time and dose-dependent and was reported in almost 50% of patients receiving HCQ in dosage of 800 mg/day and 1200 mg/day compared to 37 % in patients receiving 400mg/day of HCQ during first 6 weeks of initiation of therapy. From 7-24 weeks of HCQ treatment lesser G.I. side effects were noted in all groups due to development of tolerance[15]. As participants in present study took only 400 mg dosage of HCQ per week as compared to every day intake in study by Frust et al, much lesser incidence of G.I. side effects in the initial weeks of treatment were reported.

Literature suggest dermatological side effects is seen with 3 to 30 % of patients receiving HCQ[16]. In contrast, we observed cutaneous side-effects only in 2 HCWs; one diagnosed to have psoriasis experienced exacerbation of skin lesions with the first dose and the other complained of skin rashes along with palpitations. Sharma et al found that adverse dermatological events depend on the cumulative dose of HCQ and aetiology of condition for which it is administered[17]. Most of the adverse events were seen after treatment of autoimmune conditions over a wide range of cumulative dosage of HCQ. As in the present study the majority of participants did not have comorbid autoimmune conditions, there was lesser occurrence of cutaneous side-effects.

The most severe and life-threatening complications from use of hydroxychloroquine include QTc prolongation and the resultant risk of ventricular arrhythmias. The incidence of QTc prolongation with hydroxychloroquine use is largely unknown, as it is highly dependent on baseline ECG findings, with risk exacerbated by the use of concomitant QTc-prolonging medications, electrolyte imbalances, hepatic/renal failure and presence of structural heart disease[18]. In a study of healthy participants, QT prolongation with CQ was found to be dose dependent. An average QTc increase of 16ms (95% CI: 9-23ms) was observed with 600 mg of CQ, while 1500 mg chloroquine was associated with a 28ms increase (95% CI: 18-38ms), with the most significant QTc prolongation four hours after the second dose[19]. Studies related hydroxychloroquine and QTc prolongation are largely limited to case reports of chronic use[20].

The risk of QTc prolongation with HCQ is enhanced by coadministration of another QTc prolonging drug. Therefore, additional vigilance is required when drugs such as azithromycin, antihistaminics, digoxin, amiodarone, antiepileptics, antidepressants, antipsychotics and ondansetron are used along with HCQ[21].

When HCQ is considered for prophylaxis against COVID-19, it has been suggested to obtain baseline ECG especially in high-risk individuals. In our present study only 12 HCWs with underlying hypertension and/or diabetes reported to obtain baseline ECG prior to initiation of prophylaxis. Five participants disclosed to develop palpitations and one participant reported prolongation of QTc interval on ECG leading to discontinuation of drug.

Other cardiovascular adverse events associated with HCQ are cardiomyopathy and development of congestive heart failure which are seen with long term use of HCQ[22]. Male sex, increased age, concurrent NSAIDS and underlying diseased state were identified to contribute to the risk of cardiotoxicity in SLE and RA patients[23].

The other rare serious adverse effects of HCQ includes retinal toxicity, neuromuscular toxicities and psychiatric side-effects. Retinopathy is rare but serious complication commonly reported with long term use of HCQ. The key risk factors for HCQ related retinopathy are total dose (daily dose of >400 mg or > 6.5mg/kg/body weight; cumulative dose of > 1000gm) and duration of use (> 5 years) as well as renal or liver dysfunction, pre-existing retinopathy, age> 60 years[24] . It is not known whether exposure to lower doses of HCQ for short period of time can cause any retinal damage. In the present study although eye examination of participants was not done; none of the HCWs reported any visual disturbances.

There are few sporadic reports of HCQ induced myopathy; however, the incidence is low and it has been described only with long term use of drug[25].

HCQ and CQ rarely may also produce undesirable psychiatric side effects in patients with estimated risk ratio of 1:13,600[26]. Most of the data in literature are related to CQ and its use has been rarely reported to be associated with psychosis, depression, personality changes, suicidal behaviour, anxiety disorder and delirium. Weak evidence suggests a possible association of HCQ exposure and increased suicidal ideation[27]. It is not clear whether patients with underlying psychiatric illness are more susceptible to neuropsychiatric manifestations of these drugs. In the current study only limited assessment of psychiatric side effects were carried out by asking about nervousness, anxiety, mood swings and hopelessness. Hence the possibility of psychiatric effects with chemoprophylactic dose of HCQ cannot be ruled out. Further studies focussing

on neuro- psychiatric effects of HCQ are needed to determine their association and magnitude.

We found that younger age, co-morbid conditions, dose lesser than 1gm of HCQ and being nursing staff are significantly associated with more risk of adverse events following HCQ intake. As majority of our participants were < 40 years of age (78.2%), more side effects were reported in younger age.

In the present study 6 out of 7 participants reported taking dose of HCQ < 1 gram; experienced adverse events with first week's dose (400 mg or 800 mg; cumulative dose < 1 gram) which led to discontinuation of further HCQ ingestion. Lack of side effects or tolerance with initial loading dose of HCQ promoted adherence to subsequent weeks of drug regime.

The reason for high incidence of adverse events in nurses compared to other HCWs is not clear. Probable explanations for this observation include higher workload and longer working hours, frequent night shifts among critical care nurses compared to other HCWs which can lead to stress and greater prevalence of high burnout in them[28]. Burnout has been linked to serious physical consequences such as musculoskeletal pain, gastrointestinal issues, headache, fatigue and cardiovascular disorders[29].

The present study has many limitations; it was a telephonicsurvey and when interviewed, many participants had already completed course of HCQ prophylaxis, hence there is a concern for memory recall errors. The study included a small number of HCWs from single health centre and enrolled only those involved in direct patients care; future studies with larger sample sizes and involving all grades of HCWs are warranted for corroboration of results. As majority of participants in present study were healthy and young, hence the results need to be carefully extrapolated for older HCWs and those having co-morbid conditions.

Conclusion:

There incidence of adverse events when HCQ is used as prophylaxis against COVID-19 by HCWs is found to be 27.2%. The reported adverse events are predominantly self-limiting with no serious cardiovascular or ophthalmological or any other serious risk. Younger age and presence of co-morbidities have been found to linked to increased risk of adverse events. However further studies with large sample size are required for validating results of current study.

References

1. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (covid-19) outbreak in China. Summary of a report of 72314 cases from the Chinese centre for disease control and prevention**.** JAMA (2020), 10.1001/ jama.2020.2648 [published online 24 February]
2. Chirico F, Nucera G, Magnavita N. COVID-19: Protecting healthcare worker is a priority. Infect Control Hosp Epidemiol. 2020 Apr 17: 1. Published online 2020 Apr 17. doi: 10.1017/ice.2020.148
3. Bienvenu AL, Marty AM, Jones MK, Picot S. Systemic review of registered trials of hydroxychloroquine prophylaxis for COVID-19 health care workers at the first third of 2020. One health. Available online 19 May 20202, 100141. https://doi.org/10.1016/j.onehlt.2020.100141
4. Chatterjee P, Anand T, Singh KJ, Rasaily R, Singh R, Das S et al.Health care workers and SARS-COV-2 infection in India: A case control investigation in the time of COVID-19. Indian J Med Res 2020. Ahead of print. DOI: 10.4103/ijmr.IJMR_2234_20
5. Ministry of Health and Family Welfare, Government of India. Advisory on the use of hydroxy-chloroquine as prophylaxis for SARS-CoV-2 infection.Available at https://www.mohfw.gov.in /pdf/AdvisoryontheuseofHydroxychloroquinasprophylaxisforSARSCoV2infection.pdf [updated 22 April 2020]
6. Al-Bari MAA. Chloroquine analogues in drug discovery: new directions of uses, mechanisms of actions and toxic manifestations from malaria to multifarious diseases. J Antimicrob Chemother 2015;70:1608-21
7. Andreani J, Le Bideau M, Duflot I, Jardot P, Rolland C, Boxberger M et al. *In vitro* testing of combined hydroxychloroquine and azithromycin on SARS-CoV-2 shows synergistic effect.Microb Pathog 2020 Aug;145:104228. Published online 2020 Apr 25. doi: 10.1016/j.micpath.2020.104228
8. Vincent MJ,Bergeron E,Benjannet S,Erickson BR, Rollin PE, Ksiazek TG et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J. 2005; 2: 69. Published online 2005 Aug 22. doi: 10.1186/1743-422X-2-69
9. Rathi S, Ish P, Kalantri A, Kalantri S. Hydoxychloroquine prophylaxis for COVID-19 contacts in India. Lancet Infect Dis. 2020 Apr 17.doi: https://doi.org/10.1016/S1473-3099(20)303 13-3
10. Tilangi P, Desai D, Khan A, Soneja M. Hydroxychloroquine for high- risk COVID-19 contacts in India. Lancet Infect Dis. 2020 May 22. doi: 10.1016/S1473-3099(20)30430-8 [Epub ahead of print]
11. Ruiz-Irastorza G, Ramos-Casals M, Brito-Zeron P, Khamastha MA. Clinical efficacy and side effects of antimalarials in systemic lupus erythematous: a systemic review. Ann Rheum Dis 2010; 69:20-8
12. Nagaraja BS, Ramesh KN, Dhar D, Mondal MS, Dey T, Saha S et al. HyPE study: hydroxychloroquine prophylaxis-related adverse events' analysis among healthcare workers during COVID-19 pandemic: a rising public health concern. J Public Health 2020;42:493-503
13. Wang C, Fortin PR, Li Y, Panaritis T, Gans M, Esdaile JM. Discontinuation of antimalarial drugs in

systemic lupus erythematosus. J Rheumatol1999; 26:808-15

14. Tutor-Ureta P, Yebra-Bango M. Los antimala´ricos en las enfermedades siste´micas. Rev Clin Esp 2005; 205: 230–232
15. Furst DE, Lindsley H, Baethge B, Botstein GR, Caldwell J, Dietz F et al. Dose-loading with hydroxychloroquine improves the rate of response in early, active rheumatoid arthritis: a randomized, double-blind six-week trial with eighteen-week extension. Arthritis Rheum 1999; 42:357–65.
16. Giménez García RM, Carrasco Molina. Drug induced hyperpigmentation: review and case series. J Am Board Fam Med 2019;32(4):628-638
17. Sharma AN, Mesinkovska NA, Paravar T. Characterising the adverse dermatologic effects of hydroxychloroquine: a systematic review. J Am Acad Dermatol 2020; 83:563-78
18. Jankleson L, Karam G,Becker ML, Chinitz L A, Tsai MC.QT prolongation, torsades de pointes, and sudden death with short courses of chloroquine or hydroxychloroquine as used in COVID-19: A systematic review. Heart Rhythm. 2020 May 11 doi: 10.1016/j.hrthm.2020.05.008 [Epub ahead of print]
19. Mzayek F, Deng H, Mather FJ, et al. Randomized dose-ranging controlled trial of AQ-13, a candidate antimalarial, and chloroquine in healthy volunteers. PLoS Clin Trials 2007; 2: e6.
20. O'Laughlin JP, Mehta PH, Wong BC. Life threatening severe QTc prolongation in patient with systemic lupus erythematosus due to hydroxychloroquine. Case Rep Cardiol 2016; 2016:4626279.
21. Meid AD, Bighelli I,Machler S, Mikus G, Carra G, Castellazi M et al. Combinations of QTc-prolonging drugs: towards disentangling pharmacokinetic and pharmacodynamic effects in their potentially additive nature. Ther Adv Psychopharmacol 2017;7:251-64
22. Oren O, Yang EH, Gluckman TJ, Michos ED, Blumenthal ES, Gersh BJ. Use of chloroquine and hydroxychloroquine in COVID-19 and cardiovascular complications. Circ Arrhythm Electrophysiol 2020. https://doi.org/10.1161/ CIRCEP.120.008688
23. Cohen IV, Makunts T, Moumedjian T, Issa M, Abagyan R. Determinants of cardiac adverse events of chloroquine and hydroxychloroquine in 20 years of drug safety surveillance. Available from https://www.medrxiv.org/content/10.1101/2020.05.19.20107227v1.full.pdf
24. Ding HJ, Denniston AK, Rao VK, Gordon C. Hydroxychloroquine -related retinal toxicity. Rheumatology 2016; 55:957-67
25. Carvahlo AAD. Side effects of chloroquine and hydroxychloroquine on skeletal muscle: a narrative review.Curr Pharmacol Rep 2020;6:364-72
26. Phillips-Howard PA, ter Kuile FO. CNS adverse events associated with antimalarial agents. Fact or fiction? Drug Saf 1995; 12:370-83
27. Hamm BS, Rosenthal LJ. Psychiatric aspects of chloroquine and hydroxychloroquine treatment in the wake of coronavirus disease-2019: psychopharmacological interactions and neuropsychiatric sequelae. Psychosomatics 2020; 61:597-606
28. Saravanabavan L, Sivakumar MN, Hisham M. Stress and burnout among intensive care unit healthcare professionals in an Indian tertiary care hospital. Indian J Crit Care Med 2019; 23:462-6
29. Salvagioni DAJ,Melanda FN, Mesas AE,Gonzalez AD, Gabani FL, De Andrade SM. Physical, psychological and occupational consequences of job burnout: a systematic review of prospective studies. PLoS One 2017;12:e0185781. doi: 10.1371/ journal.pone.0185781