# The COVID-19 hydroxychloroquine prophylaxis perception of Indian anesthesiologists: A survey-based original article

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#### **Abstract**

**Background and Aims:** HCQ gained importance following the National Task Force advisory as an anti-SARS-Cov-2 (coronavirus disease-2019 [COVID-19]) drug for frontline healthcare workers (including anesthesiologists). Report of a young anesthesiologist in Assam developing cardiac arrest following HCQ intake for COVID-19 prophylaxis made us even more concerned. A conscious decision has been made by a large majority among us—to have or not to have HCQ. However, less severe complications such as gastrointestinal upset, skin-rash, visual-disturbance, headache, and dizziness even if experienced by HCQ users were likely to go unreported unless shared. The present survey was conducted to assess the prevailing perception among Indian anesthesiologists about HCQ's preventive effect against COVID-19. The information has been pooled together and discussed in this study.

**Material and Methods:** A total of 247 respondents participated in this pan-India survey. The survey questionnaire was prepared using "Google Forms" and conducted via links delivered through WhatsApp and electronic-mail.

**Results:** 55.9% (138/247) of the respondents had consumed HCQ, 38% (94/247) did not, and 6.1% (15/247) were undecided at the time of responding to the survey. In total, 47 respondents who ingested HCQ reported a side-effect, gastritis being the commonest (31).

**Conclusion:** The evidence for the effectiveness of HCQ against COVID-19 in India is reportedly as strong and weak as other drugs that have been promoted. The survey highlights the reasons consumption of HCQ and represents the opinion of 247 practicing Indian anesthesiologists. It informs the benefits and side effects of HCQ, which can help others in reaching a balanced decision.

Keywords: Anesthesiologist, coronavirus, hydroxychloroquine, prophylaxis

#### Introduction

The coronavirus disease-2019 (COVID-19) or SARS-CoV-2 pandemic has scourged the world and the global death toll stands at an alarming 485187 persons, till date, and on the rise with each passing hour. [11] India is also in the grip of this pandemic. Till date (June 25, 2020) the reported cases in India are 473718 with 14907 mortalities. [21] No definitive

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treatment or preventive measures are available, but the search continues. [3]

Hydroxychloroquine (HCQ) is a remarkably versatile 4-aminoquinolone historically an antimalarial drug. It has also been used in treating other diseases such as rheumatoid arthritis, Systemic Lupus Erythematosus, and type 2 diabetes.<sup>[4]</sup> On March 22, 2020, the National Task Force (NTF) for COVID-19 released an "Advisory<sup>[5]</sup> on use of HCQ as prophylaxis for SARS-CoV-2 infection," which prompted us to conduct this survey.

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The advisory specifies the following eligibility criteria:

- Asymptomatic healthcare workers (HCW) involved in the care of suspected/confirmed cases of COVID-19
- Asymptomatic household contacts of laboratory-confirmed COVID-19 positive cases.

Anesthesiologists comprise one of the most vulnerable groups, and fall in category 1 of the advisory. Indian Society of Anaesthesiologists (ISA National) Advisory and Position Statement regarding COVID-19 has been released recently. However, The NTF advisory could not be included as it was released after the publication of this position statement.

A small French clinical trial<sup>[6]</sup> on 36 patients and a Chinese trial<sup>[7]</sup> gave favorable results for HCQ use in COVID-19 patients. With this background, the FDA had also issued an 'Emergency Use Authorization'<sup>[8]</sup> on March 28, 2020. HCQ is also being tested off-label for COVID-19.<sup>[9]</sup> Health policymakers in India have all long been supporting the use of HCQ. Even in the latest Ministry of Health and Family Welfare (MoH&FW) guidelines for home isolation, HCQ is advocated as prophylaxis for the caregivers and other family members.<sup>[10]</sup>

The percentage of respondents who consumed HCQ, refrained from consumption or were undecided during the four stages of the survey constituted the primary outcome measure. The secondary outcome measures were thought process behind HCQ-consumption and the side-effects experienced by the respondents.

#### **Material and Methods**

This constitutes a survey-based original research, cohort study, designed and commenced on March 28, 2020 (within 1 week of release of the NTF advisory). The last response was received on April 27, 2020. The participation in the survey was voluntary and included all practicing Indian anesthesiologists. Any multiple entries by respondents and those who left all questions unanswered were excluded. As no patients or patient data was involved, ethical clearance was not mandatory. The study aimed to determine the perception of practicing anesthesiologists towards HCQ-prophylaxis and the reasons for or against HCQ consumption. The primary objective of the survey is to guide anesthesiologists in making an informed decision regarding HCQ consumption by sharing the thought process behind HCQ consumption and its side effect profile in the respondents.

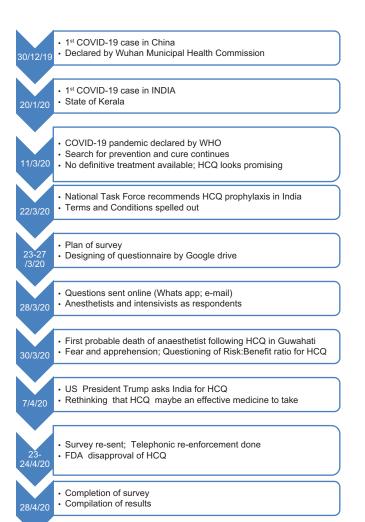
The survey questionnaire was prepared using "Google Forms" and conducted via links delivered to practicing anesthesiologists through WhatsApp and electronic-mail. Every respondent was also requested to forward the survey to their anesthesiologist friends and colleagues.

During the course of this survey, it was observed that various events have taken place which could influence the decision of HCQ consumption. The timeline for these key-events while conceiving, conduct, and analysis of the survey is provided in Figure 1. All categorical variables were expressed as numbers and percentages using line charts and tables. This is a single-arm cohort study and does not involve a comparison of two groups or subgroup analysis.

#### Results

A total of 253 responses were received. Four responses were excluded from the survey because all questions were left unanswered. Two more respondents were excluded because they filled the survey twice. Thus, a total of 247 responses were assessed.

The 247 respondents analyzed have an almost pan-India distribution with representation from 21 states and 3 union territories, [Figure 2]. Six out of the eight north-eastern states had no respondents. On the day of compilation of the results (May 1, 2020) 5 of these nonrespondent states had been declared corona-free (completely untouched by corona/with one/two COVID-19 positive cases who have now recovered).[11]



**Figure 1:** Timeline depicting stages of survey (COVID-19 = coronavirus-2019 disease, FDA = Food and Drug Administration; HCQ = hydroxychloroquine, WHO = World Health Organization)

As it was not mandatory to answer each question in the survey, some columns were left unanswered by the respondents. The total responses for each query have been indicated. Demographic information pertaining to field of anesthesia practiced and the number of years of experience have been tabulated [Table 1].

Of the 247 respondents, 138 respondents consumed HCQ, 94 respondents did not and 15 were undecided.

Four sequential key-events occurred (spanning over one month) between initiation and compilation of this survey which could have influenced the decision of the respondents on HCQ consumption. The results are accordingly assessed in these phases [Figure 3].

#### Phase 1: March 28-March 30, 2020

Release of NTF advisory—Death of anesthesiologist probably due to HCQ.<sup>[12]</sup>

There were 68 respondents (68/247; 27.5%) during this period. Of these 29 (29/68; 42.6%) took HCQ while 33 (34/68; 50%) had taken a conscious decision for not consuming HCQ, five (5/68; 7.4%) were undecided. Nine out of the nonHCQ respondents could not procure HCQ due to limited availability in the market, which was the reason behind nonconsumption.

#### Phase 2: March 30—April 7, 2020

There were 78 respondents during this period. 42 (42/78; 53.8%) consumed HCQ, 33 (33/78: 42.3%) had not taken HCQ and 3 (3/78; 3.8%) were undecided.

Fear and panic that ensued after news of death of an anesthesiologist in Assam, probably after HCQ-consumption, could have reduced consumption of HCQ. It's important to note that although many institutions had provided HCQ in their hospital pharmacy for their staff by now, some abstained from using it.

Table 1: Demographic parameters

Parameter	Percentage and absolute numbers		
Years of	<5	16.4% (40/244)	
experience	5-10	17.6% (43/244)	
	>10	66% (161/244)	
Institutional affiliation	Single institution; full time	83.3% (204/245)	
	Not fixed to a single institution	16.7% (41/245)	
Field of specialization	General anesthesia (OBG; and general surgical)	61.3% (149/243)	
	Intensive care	35.8% (87/243)	
	Neuroanesthesia	31.3% (76/243)	
	Oncoanesthesia	21.8% (53/243)	
	Pain and palliative care	11.5% (28/243	
	Cardiac anesthesia	5.8% (14/243)	
	Paediatric anesthesia	1.2% (3/243	
	Emergency medicine	0.8% (2/243)	
	Internal medicine/diabetes	0.8% (2/243)	
	Ophthalmic anesthesia	0.4% (1/243)	

#### Phase 3: April 8-April 24, 2020

There were 77 respondents during this period. Fifty-five (55/77; 71.4%) consumed HCQ while 16 (16/77; 20.8%) had not taken it and six (6/77; 7.8%) were undecided.

#### Phase 4: April 24-April 27, 2020

There were 24 respondents. 12 (12/24; 50%) consumed HCQ while 11 (11/24; 45.8%) had not taken it and one was undecided.

Overall results show that 92.7% (229/247) of the respondents were already aware of the ICMR COVID-19 advisory and 7.3% (18/247) came to know about it from the link provided in this survey. HCQ-prophylaxis was taken by 56% (138/247) respondents, 38% (94/247) had not taken HCQ while 6% (15/247) were undecided.

Of the 138 respondents who consumed HCQ, some of them had more than one reason to convince them to consume HCQ.

The reasons for consumption of HCQ are summarised in Table 2.

At least two respondents considered HCQ to be a safe drug. Out of these, one respondent had a personal experience of using it for treating fever empirically while another one although not convinced about its benefit considered it worth trying looking at the safety profile of the drug. Both did not develop any side effects after HCQ consumption.

Out of those who consumed HCQ (138 respondents), 86 did not develop any side-effects. 47 developed side effects and 5 did not respond to the query. Gastrointestinal (GI) symptoms was the commonest side-effect observed in 31/47 [Table 3].

One respondent developed severe myalgia, malaise, and diarrhea after the loading dose of HCQ which continued into the second week, though reduced in severity. He also developed Herpes zoster in the second week, and was treated with valacyclovir.

15 respondents developed more than one side-effect.

#### Opinions of the respondents

A review of opinions revealed that the respondents put in efforts and had given serious thoughts on the matter.

It is informed that Internet search, was frequently used by the respondents. Quoting the responses, it was observed that decisions were also taken "after attending AIIMS webinar, discussion with friends working in CDC, discussion with friends in UK who had not taken HCQ, reading, articles received from colleagues, seeking expert opinion from pulmonologists, Infectious Disease expert in CMC Vellore and a search in textbook of pharmacology".

While many of the suggestions given are already reported in the literature, some respondents gave certain unique

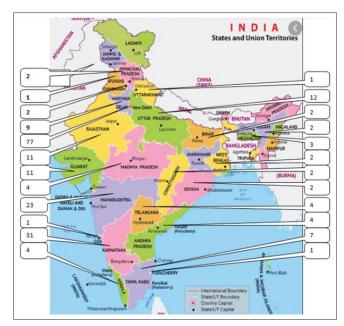


Figure 2: Nationwide representation of respondents

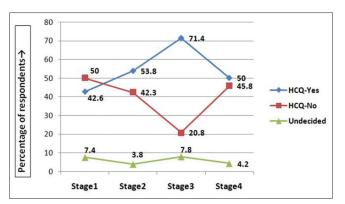
observations and suggestions which deserve special mention and are stated.

Of the 247 respondents, 138 respondents consumed HCQ while 94 respondents did not consume HCQ. Majority (201/247) had definitive opinion—YES or NO for HCQ consumption, while (15/247) respondents were undecided on prophylactic intake of HCQ, and had not consumed HCQ at the time of filling up the survey.

109 respondents maintained that there is no convincing evidence to support HCQ intake. Out of this 31 consumed HCQ despite not being convinced and 78 did not.

Some respondents opined "With paucity of testing, continuous exposure as an HCW, vulnerable family members at home and symptoms of upper respiratory tract infection, the best available option was to decrease their viral load with HCQ. Some respondents were skeptical on HCQ prophylaxis and gave their own reasoning. Six respondents feel it isn't the right step, out of which two feel it is like blunting own immunity to prevent the virus-related cytokine storm. One opined that "guidelines like the present one gives false sense of confidence or add to confusion".

Suggestions were also put forth on who should consume HCQ: While 7 respondents feel that it's better that all must take HCQ prophylaxis rather than risk oneself of developing severe symptoms, 34 feel that HCQ should be used only by HCW at high risk, or those involved in COVID-19 care and not as a blanket prophylaxis. While 7 believe that with good quality PPE and good infection-control practices HCQ prophylaxis is not required, 34 opine to reserve HCQ intake only after exposure to a COVID-19 patient or developing upper respiratory tract infection (URTI) during pandemic.



**Figure 3:** Percentage of respondents, who had consumed HCQ, refrained from consumption or were undecided during the four stages of the survey (HCQ = hydroxychloroquine)

Table 2: Reasons behind HCQ consumption			
Reason for HCQ consumption* (*Seven questions asked in the survey questionnaire)	Number		
My personal decision: I am a strong believer in following guidelines	64		
After extensive search on Internet I got convinced it's worthwhile taking it	63		
Pressure from my family members	7		
Peer pressure from my doctor friends and colleagues	21		
I got exposed to SUSPECTED COVID-19 patient	6		
I got exposed to a KNOWN COVID-19 positive patient Others	1		
Apprehensions of unknowingly getting exposed to COVID-19 positive patient (working in an ICU with patients on ventilator support)	7		
Not much harm in taking HCQ	1		
After reading and consulting respiratory medicine physician	1		
HCQ tablets provided by the institution; institution may refuse insurance if HCQ not taken; Hospital policy for all anesthetists	3		

HCQ = hydroxychloroquine

Issues related to availability of HCQ were also informed: Two respondents had taken an initial dose and another 10 expressed willingness to start HCQ but because of nonavailability could not consume HCQ. Four opined that HCQ should be made available to all HCWs by the institution/hospital.

Some suggested on need of additional scientific evidence on role of HCQ for COVID-19. Two respondents would like to conduct their own mini clinical trials like follow-up for 8 weeks in persons who have taken HCQ and compare with HCWs who did not take it. Another 5 respondents would take HCQ only if they become symptomatic but would prefer to wait till convincing evidence is available in the form of clinical trials. One opines that as doctors we should volunteer ourselves for a randomized controlled trial (RCT) to generate evidence.

The suggestions also were given related to HCQ safety. It was suggested "to get baseline ECG prior to HCQ consumption (seven respondents) to ascertain QTc interval" and a detailed physician "evaluation for low left ventricular

Table 3: Side effects plotted against the number of respondents who developed them

Side effect	Number of respondents
Gastritis	31
Headache	5
Dizziness	4
Myalgia	4
Weakness	3
Nausea	2
Abdominal pain	2
Rashes	2
Sleepiness/lethargy	2
Tinnitus	2
Menorrhagia	1
Petechiae on the legs	1
Throat pain	1
Anorexia	1
Altered taste	1
Breathlessness and palpitations	1

ejection fraction. "Beta- blocked, diabetic, and allergy-prone individuals should avoid HCQ" (one respondent). "A repeat ECG prior to every subsequent HCQ dose" was suggested by one respondent), while another respondent suggested that "pharmacovigilance inputs can also be given at local centers and glucose-6-phosphate dehydrogenase (G6PD) test and retinal check should also be done". One anesthesiologist who has psoriasis did not take HCQ out of fear of aggravating it but would take HCQ if exposed to a COVID-positive individual.

Some feel the need for modification of the NTF regimen (6 respondents). One respondent suggested an increasing gap between the two doses (loading) from 12h to 18h, followed by 400 mg weekly. We also have a prevalence map that shows COVID-19 is not rampant in malaria-infested areas. If at all we intend to use HCQ-prophylaxis it should be used as we use in malaria. A respondent opines that, "such unprecedented mass consumption of HCQ pan-India and even the entire world might have a long-term effect on other viruses, malaria resistance and immune response."

Based on social media, three respondents opted for alternatives such as Vitamin-C (1-2g per day), Vitamin-E, and zinc intake instead of HCQ as immunity boosters. One respondent cites HCQ opening cellular gateways for zinc, resulting in zinc stopping viral replication; hence, both be used in conjunction.

#### Discussion

The present survey was almost a pan-India survey spanning 21 states and 3 union territories and represents the perceptions of 247 practicing Indian anesthesiologists and intensivists. It is known that this subset of professionals has an exceptionally high risk. The opinion was polarised regarding whether or not to consume HCQ, before 7/4/20. Most (55/77) of the respondents who took the survey after this date were in favor

of taking HCQ. This phenomenon could be the effect of rising paranoia across the globe<sup>[13]</sup>, and also could be associated with a rising corona count in India.

Quinine mixed with juniper-based gin (to nullify the bitter taste) was consumed in India as a tonic by British soldiers reeling under an onslaught of malaria. [14] The mechanism of action [15] of this multipurpose drug is not completely understood. HCQ by interacting with Toll-like receptors TLR3/4, hampers activation of synovial fibroblasts while its action on TLR7/9 inhibits TNF-production. One of these mechanisms may provide pre- and post-exposure prophylaxis to COVID-19.

The side effects<sup>[16-18]</sup> reported are retinopathy, ototoxicity, prolongation of QT-interval, hypoglycemia besides nausea, vomiting, and gut irritation. If doses are kept below 6.5 mg/kg, HCQ appears to be relatively safe and free from these side-effects.<sup>[19]</sup>

One patient had developed Herpes Zoster which could be because of immune suppression after HCQ.

The role of HCQ in treatment of COVID-19 infection continues to be equivocal. It is as good or bad as any other drug under trial. Each day reports on use of HCQ with benefits and otherwise are being reported/published. [5-7,13,15,16-20]

During the course of the survey, there have been certain key events as mentioned previously which could have influenced the respondents' decision for/against HCQ-prophylaxis for COVID-19. The results have been accordingly discussed against this background.

However, HCQ is still not out of use. Clinical trials of HCQ in combination with other medications are still in progress. The efficacy of HCQ (or lack of it) in treating COVID-19 will be established only once the results of these studies are known.

#### Strengths of the survey

It's the first survey after the release of the NTF advisory. Secondly, the respondents are Practicing Indian Anesthesiologists who are known to be at higher risk of COVID-19 infection. So, any good prophylaxis would be readily acceptable. Lastly, respondents from almost all states of India were included.

This survey comes at a time with existing confusion and conflicting opinions regarding HCQ ingestion. The opportune timing of our survey, its almost pan-India representation and the large number of respondents constitute the major strengths of the survey. Our survey has the potential to guide anesthesiologists in making an informed decision regarding HCQ consumption by sharing the thought process behind HCQ consumption and its side effect profile in the respondents.

#### Limitations of the survey

This survey was conducted soon after the consumption of HCQ following the NTF advisory. The intermediate and

long-term effects after 7 weeks of consumption, if any, could not be ascertained.

The major limitation is that four major events all backtracking the previous one has not left the respondents with a common batting-field. In other words, the same respondent may have answered differently in each of the four stages described in the results section. Many Phase-I or II respondents who had initially answered with a thumbs-down for HCQ might have given HCQ a thumb—up had they responded in Phase-III instead. Conversely, many phase I or II respondents who had initially answered with a thumbs-up for HCQ might have given HCQ a thumb-down had they responded in Phase-IV instead.

The study is likely to arouse interest at the microbiological, biochemical, and outcome-study levels and initiate several randomized controlled trials involving HCQ, contributing to future research.

#### **Conclusion**

The evidence for effectiveness of HCQ against COVID-19 in India is reportedly as strong and weak as other drugs that have been promoted.<sup>[21]</sup> Even the revised guidelines for Home Isolation of very mild/pre-symptomatic COVID-19 cases released by MoH&FW, reiterated the Government of India's stand and support to HCQ[10] However, it's a personal decision, that needs to be taken after considering potential side-effects and existing comorbidities. HCQ is used in malaria-endemic regions of India and has known side-effects in anti-malarial doses. The knowledge that HCQ may prevent life-threatening pneumonia even if we contract COVID-19 infection may be a boon for HCW. A likely fatality is converted into an upper respiratory disease which resolves over a few weeks. However, there is a word of caution over concomitant use of drugs prolonging QT-interval and in HCW with co-morbidities.

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#### Conflicts of interest

There are no conflicts of interest.

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### **Appendix**

#### Survey questionnaire

#### (A) YOU & YOUR INSTITUTION

- 1. Name
- 2. Your Age in years
- 3. Email id and mobile number
- 4. Experience after specialization:
  - a. <5 years
  - b. 5-10 years
  - c. > 10 years
- 5. Institution Address
- 6. Your practice is
  - a. Full time in one institution
  - b. Not fixed to a single instituion. I work in more than one hospital
- 7. You are presently practising:
  - a. General Anesthesia (Genral surgery, Obs/Gyn, Ortho)
  - b. Neuro-anesthesia
  - c. Cardiac Anesthesia
  - d. Onco-anesthesia
  - e. Intensive Care/Critical Care
  - f. Pain & Palliative Care
  - g. Retired: Not working at present
  - h. Other:

#### (B) COVID-19: YOUR UNDERSTANDING & EXPERIENCE

- 1. Are you aware of The National Task Force for COVID-19 advisory (ICMR advisory) on HCQ stated above
- a. Yes
- b. No
- c. Learnt about the advisory from the link in this survey
- Have you taken/started yourself on the HCQ as per the advisory
  - a. Yes
  - b. No
  - Undecided till now
- What made you decide to start HCQ prophylaxis as stated in advisory
  - a. My personal decison: I am strong believer in following guidelines.
  - b. After extensive search on the Internet I got convinced its worthwhile taking it
  - c. Pressure from my family members
  - d. Peer pressure from my doctor friends and colleagues
  - e. I got exposed to SUSPECTED COVID-19 patient
  - f. I got exposed to a KNOWN COVID-positive patient
  - g. Other:
- 4. If YES, and you consumed HCQ, did you develop any side effects which you feel were due to HCQ consumption? Please inform in brief
- 5. Despite being aware of the guidelines, I decided AGAINST THE USE of HCO because:
  - a. I have underlying co-morbid conditions (cardiac ailments etc) for which I feel I must avoid
  - b. I have an underlying ophthalmic ailment. HCQ is known to cause ophthalmic side effects
  - Nonavailability of HCQ : I tried but could not get it
  - d. As HCQ was not available, i consumed chloroquine instead

- e. I did not take it because I was not convinced on its prophylavctic value
- f. The drug I feel has untoward side effects: Risks are more than the benefit
- g. I feel at my age I must avoid intake of HCQ
- h. After extensive search on the Internet, I got convinced its NOT worthwhile taking HCQ
- i. Other:
- 6. References you have used to reach your decision on Use or Not to Use HCQ. (Please paste the links you assessed)
- 7. Your opinion/suggestion on this matter