Original Article

Prophylaxis with Chloroquine and Hydroxychloroquine in Covid-19

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Received: Jan 12 2020

Accepted: Feb 20 2020

Citation to this article:

Janatalipour A, Jazaeri S, Hadadi A. Prophylaxis with Chloroquine and Hydroxychloroquine in Covid-19. *J Iran Med Counc*. 2020;3(1):2-8.

Abstract

Background: Since December 2019, an emerging virus called SARS-CoV-2 has spread in Wuhan, China, and has now become a global "pandemic" with the development of a disease called Covid-19. High emission capability and significant mortality of this disease indicate the need for immediate and effective attention to this issue. So far, many efforts have been made to introduce an effective treatment for Covid-19. Due to the contagiousness and high prevalence of the disease, chemoprophylaxis is a topic of discussion that is frequently asked by people and medical staff. The most suitable of the proposed drugs for this purpose are Chloroquine and Hydroxychloroquine which, besides anti-malarial and anti-inflammatory effects, have also antiviral effects. However, for introducing these drugs as prophylaxis, more evidence is needed.

Methods: In this study, the existing articles and studies on the use of Chloroquine and Hydroxychloroquine as an effective drug in the prevention of Covid-19 have been studied. References used in this review were identified through a search of PubMed and Google Scholar with keywords of "Hydroxychloroquine", "Chloroquine", "COVID-19", "COVID 19", "2019-nCoV", "2019-CoV", "coronavirus", " SARS-nCoV-2", "antiviral", and "prophylaxis". Articles obtained from this search and relevant references were reviewed and included.

Results: Available studies on the pharmacological effects of Chloroquine and Hydroxychloroquine on SARS-CoV-2 have been performed in the laboratory (In vitro). Till now, 5 clinical trials have been conducted in this field and their preliminary results will be published in the next few months. There are also different prophylactic doses suggested in existing studies.

Conclusion: Due to the lack of sufficient clinical evidence and the uncertainty about the dose required to create a prophylactic effect against the disease and due to possible complications, the use of these drugs for prophylaxis is not recommended until the first results of clinical studies are published and then approved by WHO, CDC and FDA. Sufficient attention should be paid to personal protective equipment.

Keywords: Chloroquine, Covid-19, Hydroxychloroquine, Prophylaxis

Introduction

Since December 2019, an emerging virus from the coronavirus family started to spread in Wuhan, China, and has spread to dozens of other countries in a matter of months, now becoming a "pandemic" as a global concern (1). The virus is called SARS-CoV-2 and the disease caused by it is named "COVID-19" (2). According to global statistics, the number of people infected with the virus in the world has reached more than 1,200,000 till 11 April and the number of victims has reached more than 68,000 so far. In Iran, these statistics are more than 58,000 infected people and more than 3,000 victims (3). The number of affection and mortality is increasing, but due to the lack of diagnostic kits at the beginning of the crisis, the reported cases may be lower than the real statistics. There are still many unknowns about the mechanism of action of the virus, the symptoms of the disease, the prevention and treatment of the disease.

Mechanism of action of coronavirus

The corona virus relies on spike proteins on its surface to bind to receptors on the host cell surface. In the case of the emerging coronavirus, this receptor is called Angiotensin-Converting Enzyme-2 (ACE2), which is not only expressed in alveolar epithelial cells, but also in the heart, gastrointestinal tract, kidney, testis and other organs, which means that SARS-CoV-2 is likely to enter other tissues and organs through ACE2 binding, causing multiple organ damage (4). Virus endocytosis for entering the host cell depends on the acidic pH of the endosomes. Once the virus enters the host cell, its RNA binds directly to the host's ribosome to express two large proteins, which are later converted by proteolysis to elements to form virions. The two main proteases involved in this process are coronavirus main proteinase (3CLpro) and papain-like protease (PLpro). On the other hand, for RNA genome transcription, the virus encodes a replica called RNA-dependent RNA polymerase (RNA). Drugs used today to treat Covid-19 have also targeted the same four components (Spike 3CLpro, PLpro, RdRp) (5).

Asymptomatic carrier

Symptoms of Covid-19 consist of spectrum of fever, sore throat, dry cough, chest pressure, dyspnea, diarrhea, abdominal pain, nausea, vomiting, headache, disturbance of taste and smell and in severe cases, Acute Respiratory Distress Syndrome (ARDS). A group of patients also have no signs or symptoms of the disease, which are referred to as asymptomatic carriers. These patients are only positive for the Polymerase Chain Reaction (PCR) test for coronavirus (6). According to the American Centers for Disease Control and Prevention (CDC), healthcare workers or those who have been in close contact with a suspected or confirmed Covid-19 patient for the last 14 days are indicated for PCR testing of oropharyngeal or nasopharyngeal sample. Close contact is defined as being within approximately 6 *feet* (2 *meters*) of a COVID-19 case for a prolonged period of time or having direct contact with infectious secretions of a COVID-19 case (*E.g.*, being coughed on) without personal protective equipment (*E.g.*, gowns, gloves, mask, eye protection). Close contact can occur while caring for, living with, visiting, or sharing a healthcare waiting area or room with a COVID-19 case (7).

Pharmacological prophylaxis

Given that no definitive treatment has been proposed for the new coronavirus, using preventive measures will be helpful to control the pandemic. In the meantime, one of the most important issues is to identify asymptomatic carriers among the healthcare workers and other members of the community, because due to the contact of these people with vulnerable groups, it is possible to infect them as much as possible and consequently to increase the cost imposed on the medical system and patients. Non-pharmacological interventions approved so far to control the Covid-19 epidemic include home isolation, home quarantine, and avoidance of gatherings especially for the elderly, and temporary closure of schools, universities, and offices (8). The use of chemoprophylaxis or pharmacological prevention as one of the most important and effective strategies for controlling pandemics is associated with many challenges. In the case of some other viral and microbial diseases, prevention with antimicrobial drugs was effective in the prevention of the disease; "pre-exposure prophylaxis" is a method used to prevent the disease before exposing to the probable cause and "post-exposure prophylaxis" is

documented exposure to microbial agents in order to reduce the risk of secondary infection (9). In general, the four main methods of chemoprophylaxis for infection control in pandemics include vaccination, intravenous immunoglobulin (IVIG), plasma exchange of affected patients, and the use of micro molecular drugs (10). The production of vaccine will cost millions of dollars and will be operational in the next 12-18 months at best. To date, there have been no proven reports of using antiviral drugs for Covid-19 prophylaxis, but they have been discussed earlier for some viral infections such as influenza (11), AIDS (12), and cytomegalovirus (13) for pre and post exposure to the virus. There was also scientific and theoretical evidence for the therapeutic effect of Chloroquine on influenza in 2006 (14) ; however, the study of its prophylactic effect on rodents failed in 2013 (15) and also clinical trials in 2011 failed to prove the efficacy of prophylactic Chloroquine for influenza (16). So, despite strong laboratory data on the therapeutic effect of Chloroquine and even its evidence in a Chinese clinical trial, Chloroquine may still be ineffective as a prophylaxis (10).

This article investigated existing papers about the chemoprophylactic effect of Hydroxychloroquine on asymptomatic carriers of Covid-19.

Materials and Methods

In order to find studies and evidence of the effectiveness of Chloroquine and Hydroxychloroquine for COVID-19 chemoprophylaxis, related databases as well as evidence-based databases including Pubmed, Uptodate and finally Google Scholar and Google were searched for possible related evidence in the period from December 1, 2019 till now.

The websites reviewed are indicated below;

1. https://www.who.int
2. https://www.cdc.gov, (CDC, Centers for Disease Control and Prevention)
3. https://clinicaltrials.gov/

For this purpose, the applied keywords were "Hydroxychloroquine","Chloroquine","COVID-19", "COVID 19", "2019-nCoV", "2019-CoV", "coronavirus", "SARS-nCoV-2", "antiviral", and "prophylaxis".

The search strategy was adjusted based on each database, and controlled keywords were searched if possible. A total of nearly 200 studies were recovered. The process of selecting articles began by screening the title, abstracts of studies, documents and after screening the abstracts, 14 articles were selected.

Results

Chloroquine and Hydroxychloroquine for chemoprophylaxis

Chloroquine and Hydroxychloroquine were recognized as anti-malarial drugs for treatment (since 1934) and prevention of malaria (since 1947) and then due to their anti-inflammatory effects were used in the treatment of diseases such as rheumatoid arthritis, lupus, systemic sclerosis, MS, Q fever, Whipple's disease, and some fungal and viral infections (17).

Chloroquine has a half-life of about 50 days (17) and has hepatic metabolism (*Via* cytochrome P450) (18).

Chloroquine and Hydroxychloroquine lead to a cascade of intracellular effects, including altered ACE2 glycosylation (cessation of spike virus binding to host cells), increased pH of endosomes and lysosomes (and subsequent inhibition of virus endocytosis by host cells), inhibition of viral genome fusion to the host and also inhibition of cytokine production (and preventing inflammatory complications) (17,18).

The following are important tips for choosing an antiviral drug as a chemoprophylaxis in epidemics:

1. Proper efficacy of the drug
2. Possibility of prescribing medicine at the right time (Pharmacokinetics and pharmacodynamics)
3. More advantages than disadvantages as well as low side effects
4. Drug availability for a large population (10)

Of the antiviral drugs available for the treatment of coronavirus, Chloroquine and Hydroxychloroquine are drugs that cover all of the above, and have therefore been considered as first line chemoprophylaxis in studies (10).

Another advantage of these drugs is that they are safe and well tolerated at regular doses. Common side effects in short-term use include nausea and vomiting, anorexia, diarrhea, abdominal pain, dizziness and headache, blurred vision, itching and in chronic use (Usually more than 5 years), they include retinopathy, cardiac, neurological and ocular complications. Contraindications of using are retinopathy and a history of drug allergy (17).

In a study comparing the effects of Chloroquine

and Hydroxychloroquine, it was found that Hydroxychloroquine had stronger antiviral effects [less EC50- (Effective concentration 50: the concentration of a drug that gives half-maximal response)] than Chloroquine in vitro (19). Hydroxychloroquine also has fewer side effects than Chloroquine (20). In association with Covid-19, the in vitro efficacy of Chloroquine and Hydroxychloroquine against coronavirus, and in particular SARS-CoV-2, has been demonstrated (9).

Previous studies of the SARS-CoV virus have shown the in vitro effectiveness of Chloroquine in preventing infection if the drug is started 24 hours before exposure and even up to 5 hours later (21). In vitro studies have shown the antiviral activity of Chloroquine with 1.13 *micromolar* EC50 in Vero cells[1] (18). However, it is not yet known how this activity occurs in the respiratory epithelial cells and inside the body (In vivo).

In the latest study (10), two options for prophylaxis with this drug were indicated [based on the drug level (in vitro) created by the routine doses of Chloroquine]:

1. Chloroquine at a dose of 8 *mg/kg/day* for three days (Equivalent to the therapeutic dose in the acute phase of malaria) as a "post-exposure prophylaxis" within a few hours of contact with infected person
2. Chloroquine at a dose of 500 *mg* daily (Equivalent to the therapeutic dose in rheumatoid arthritis) for 30 days and then 250 *mg* daily for several months (until the end of the epidemic) as "chronic prophylaxis" in people living in endemic area and are at high risk of exposure

As mentioned, the lack of animal models and adequate human studies to investigate the effects of the above drugs as prophylaxis has been the main problem in citing these reports, and all studies and conclusions have been based on experiments performed *in vitro*.

Existing clinical trials and suggestions

Numerous clinical trials have been conducted in China to study the therapeutic effect of Chloroquine on Covid-19. The preliminary results of studies on more than 100 patients showed the effect of Chloroquine on reducing disease duration, reducing the severity of pneumonia, and improving radiological findings (22). Also, various clinical trials have been designed to investigate the prophylactic effect of Chloroquine and Hydroxychloroquine in Covid-19, which are shown in table 1.

Tansan in a report (23) based on Yao *et al's* study, said that a single dose of 800 *mg* Hydroxychloroquine may provide a concentration in the lung tissue that is more than 20 times higher than the EC50 values for inhibiting SARS-CoV-2 in lung in the first day. Therefore, it is expected that a single dose of 400 *mg* or even 200 *mg* can provide sufficient concentration in lung tissue to inhibit SARS-CoV-2. Because the half-life after administration of a single dose of 200 *mg* of Hydroxychloroquine (Based on FDA data) is 22 days, a single dose every three weeks may be sufficient to prevent lung damage caused by SARS-CoV-2. Despite insufficient drug concentrations in the blood or sinuses to eradicate the virus, preventing lung damage may turn this fatal infection into an upper respiratory infection. He has suggested the use of Hydroxychloroquine as a prophylaxis as follows; all healthcare workers exposed to Covid-19 should take 400 *mg* every 12 hours on the first day and then 400 *mg* weekly for 7 weeks. Asymptomatic patients in home contact or with positive PCR should take 400 *mg* every 12 hours on the first day and then 400 *mg* weekly for 3 weeks.

Pourdowlat *et al* wrote in a paper that according to a study of patients with rheumatoid arthritis treated with 200 *mg* of Hydroxychloroquine daily and mild to moderate involvement of the group, a prophylactic dose of 200 *mg* daily with Hydroxychloroquine for healthcare workers can prevent severe disease. The required dose in post-exposure prophylaxis is also mentioned in this article as 600-800 *mg* on the first day and then 200 *mg* daily (24).

The American Medical Association (AMA) and the American Pharmacists Association (APhA) strongly opposed prescribing Hydroxychloroquine prophylaxis in a statement, citing the lack of proven evidence. Irrational prescriptions will not only lead to a lack of Hydroxychloroquine for the treatment of patients with Covid-19, but will also pose a real risk to patients with rheumatic diseases who depend on these drugs for survival (25).

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1. A lineage of cells used in cell cultures. The 'Vero' lineage was isolated from kidney epithelial cells extracted from an African green monkey

Table 1. Ongoing clinical trials investigating the prophylactic effect of Chloroquine and Hydroxychloroquine in COVID-19

Number	Title	Location	Start date	Primary completion date	Enrollment	Intervention
NCT04304053	Treatment of Non-severe Confirmed Cases of COVID-19 and Chemoprophylaxis of Their Contacts as Prevention Strategy	Barcelona, Spain	March 18	June 15	3040 participants	Darunavir 800 *mg* / Cobicistat 150 *mg* tablets (Oral, 1 tablet q 24h, taking for 7 days) and Hydroxychloroquine (200 *mg* tablets) 800 *mg* on day 1, and 400 *mg* on days 2,3,4, 5, 6 and 7 Contacts will be offered a prophylactic regimen of Hydroxychloroquine (200 *mg* tablets) 800 *mg* on day 1, and 400 *mg* on days 2, 3, 4
NCT04303507	Chloroquine/ Hydroxychloroquine Prevention of Coronavirus Disease (COVID-19) in the Healthcare Setting	Oxford, United Kingdom	April	April 2021	40000 participants	Chloroquine or Hydroxychloroquine, a loading dose of 10 *mg* base/ *kg* followed by 155 *mg* daily (250 *mg* Chloroquine phosphate salt or 200 *mg* of/ or Hydroxychloroquine sulphate) for 3 months
NCT04318444	Hydroxychloroquine Post Exposure Prophylaxis (PEP) for Household Contacts of COVID-19 Patients	New York, United States	March	March 2021	1600 participants	Hydroxychloroquine, two tablets (400 *mg*) twice daily on day 1; for days 2-5, one tablet (200 *mg*) twice daily
NCT04308668	Post-exposure Prophylaxis or Preemptive Therapy for SARS-Coronavirus-2	Minnesota, United States	March 17	April 21	3000 participants	Hydroxychloroquine 200 *mg* tablet; 800 *mg* orally once, followed in 6 to 8 hours by 600 *mg*, then 600 *mg* once a day for 4 consecutive days
NCT04318015	Hydroxychloroquine Chemoprophylaxis in Healthcare Personnel in Contact with COVID-19 Patients	Mexico	April 21	December 31	400 participants	Hydroxychloroquine 200 *mg* per day for 60 days

has also not recommended the use of prophylaxis to prevent disease in exposed persons (26).

Discussion

According to existing studies despite available data on positive prophylactic effects of Chloroquine or Hydroxychloroquine in vitro on Covid-19, due to possible side effects and lack of specific dose required for chemoprophylaxis, it currently does not appear that drug prevention with Chloroquine or Hydroxychloroquine in Covid-19 be effective and cost-saving.

Conclusion

There is still a need to do more research in this area. The best and surest way to protect against the coronavirus is to take full protective equipment (*E.g.*, gowns, gloves, mask, eye protection) in contact with infected patients.

Acknowledgments

The authors would like to thank the staff of the Research Development Center of Sina Hospital for their help and support.

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