Review article

Myths and Facts: Chloroquine May be a Potential Supportive/Therapeutic Drug in COVID-19 Treatment

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Abstract

Quinine and its less toxic derivatives have served humanity for decades as potent antimalarial drugs. Emergence of drug resistance has narrowed the usage of these drugs in malaria prevention and treatment. Fortunately, these drugs have roles in the treatment of other diseases as well including rheumatic disorders and viral infections. Quinine derivatives have proven antiviral effects, especially against human immunodeficiency virus (HIV), Zika virus (ZiKV), herpes simplex virus (HSV), Ebola virus and dengue virus (DENV). The prophylactic and therapeutic role of Chloroquine/hydroxychroquine has become a topic of interest after the recent outbreak of novel Corona virus-19 (nCoV-19). This virus is also named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and WHO has officially named this disease as Corona virus disease 2019 (COVID-19). This lethal virus has affected almost 186 countries of the world till to date just in a period of four months of its outbreak. No approved antiviral drug is existed for the treatment of COVID-19. Therefore, this review is focused on potential prophylactic and therapeutic role of chloroquine/hydroxychlroquine for COVID-19.

Keywords

COVID-19, Outbreak, nCoV-19, Quinine, Chloroquine, Hydroxychloroquine

Introduction/background of quinine and its derivatives

During the ancient times, bark of *Cinchona* tree was used for the treatment of intermittent fever. A breakthrough happened in the history of mankind when two French chemist in 1820, isolated an active ingredient of Cinchona bark, named quinine. This discovery had become a treatment of choice for malarial fever all across the world. Still, quinine remains a potential and effective antimalarial drug, although resistance has been emerged against quinine in many parts of the world [1]. The only problem with this miracle drug was its potential side effects, but benefits of quinine outreached its drawbacks. Scientists have synthesized its less toxic derivatives chloroquine, amodiaquine and mefloquine to reduce the side effects of quinine. Actually, synthesis of quinine derivatives is based on presence of quinolone ring in the chemical structure of quinine (Figure 1) [2].

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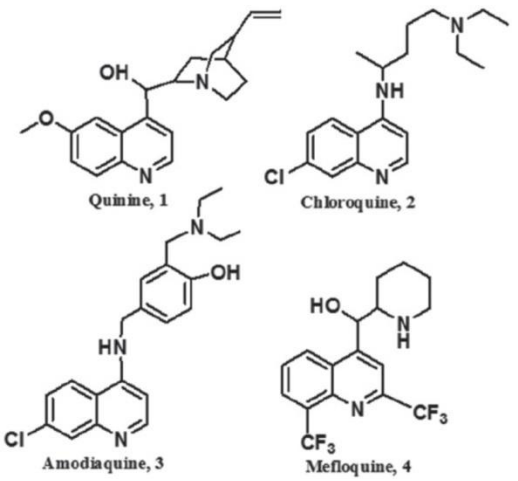

Figure 1: Molecular structure of quinine and its derivatives

Quinine and its derivatives as antiviral drugs

In spite of serving the humanity for decades, emergence of drug resistance has narrowed the usage of quinine and its less toxic derivatives in malaria prevention and treatment [3]. The beneficence story of quinine had opened up a new horizon, when scientists had reported potential antiviral effects of quinine and its derivatives. Three main reasons have been described for the consideration of antiviral role of antimalarial drugs;

i. Complex chemical structure of these drugs
ii. Shared geographic distribution of malaria and viral diseases
iii. Lack of effective vaccines and therapeutic drugs against deadly viruses [4].

The earliest documented literature regarding antiviral effects of quinine had been published in 1946, when Seeler and his coworkers studied the role of quinine against influenza in mice. They reported slight but consistent antiviral effects of quinine during the course influenza infection [5]. After this initial discovery, a number of studies have successfully established the antiviral effects of quinine and its derivatives in treating the viral pathologies including herpes simplex-1, HIV, chikungunya virus, dengue and Ebola viruses [6-12]. During Ebola outbreaks in West Africa, a number of researchers had desperately trialed multiple FDA approved drugs for the treatment of affected patients. Li et al. utilized chloroquine against Zika virus infection and they found that not only in vitro but also in mouse models, this drug effectively inhibits Zika virus and also protects embryonic brain from ZiKV infection [13]. Other than these above mentioned studies, more than hundred other studies have reported the potential antiviral role of quinine derived antimalarial drugs but problem persists because none of these drugs has been approved as antiviral

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drug from some drug regulatory agency like FDA.

Recent outbreak of novel Corona Virus (nCoV-19)

Now comes on to the recent outbreak of Corona virus infection which had been started from Wuhan city, Hubei province of China and affecting the 196 countries and territories of the world till to date more than two million cases and almost 154000 deaths just in a period of four months [14]. This outbreak was started as pneumonia of unknown cause in Wuhan city, Hubei province of China and reported to the WHO country office on 31st December 2019. On the basis of its lethal epidemic effects, WHO had declared COVID-19 outbreak as a public health emergency of international concerns on 30th January 2020 [15]. Actually, Corona virus family is a diverse and large family of viruses causing only mild illness like common cold and flu, but its current outbreak has devastating effects. Chinese authorities first identified and reported a novel type Corona virus with distinct genetic make-up and which had not been previously detected in humans or animals [16]. This virus is also named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and WHO has officially named this disease as Corona virus disease 2019 (COVID-19). This COVID-19 is considered as a contagious disease and transmitted from human to human. It is assumed that a COVID-19 patient can affect two other persons on average [17,18].

The severity of COVID-19 outbreak can be assessed by the fact that previously two reported Corona epidemics, Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV) have infected approximately 10000 individuals during the last 20 years [19]. Till to date no effective and approved drug has been developed against COVID-19/SARS-2 because this nCoV-2019 is an emerging virus. Only few evidences could be seen in the literature regarding treatment of Corona virus; i) A very historical cohort of 41 SARS patients had been trialed with a combination of antiviral drugs lopinavir/ritonavir and ribavirin. This cohort study was performed by Chu and his colleagues in 2004 with three antiviral drugs licensed for clinical use. That SARS Study Group concluded that all these three antiviral drugs had shown favourable clinical outcome and they recommended further randomized control trials in patients with SARS [20]. ii) Another historical study on Corona virus treatment

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was performed in Saudi Arabia. It was a randomized control trial on MERS patients using a combination of lopinavir/ritonavir and recombinant IFN-β1b and findings related to clinical outcome [21]. Some other studies have also reported fruitful preclinical evidence with a potent broad spectrum antiviral drug remdesivir against MERS and SARS infections [22,23].

When this current outbreak started in China and causing morbidity and mortality in 196 countries, no approved treatment has been existed even for previously identified types of Corona virus and diseased caused by them i.e. SARS and MERS. Surely this is the reason behind high mortality and rapidly rising death toll due to COVID-19. This entire situation may force the clinicians and authorities to use some safe or at least less toxic alternatives for the treatment or lessening the symptoms of COVID-1 patients to rduce morbidity and mortality rate until the availability of effective drugs and prophylactic vaccines.

Controversy regarding anti-nCoV-19 effects Chloroquine/Hydroxychlroquine

Keeping forth the option of alternative treatment strategies, discussion should be turned again towards the antiviral effects of antimalarial chemotherapeutic drugs because evidence has been existed as described above, although not sufficient. A hot debate has been started on leading news channels, newspapers, magazines and social media websites after the media talk delivered by Mr. Donald Trump, the president United States of America. That gentleman claimed that Chloroquine and Hydroxychoroquine may play game changer role in treatment of COVID-19 [24]. His statement raised a peak hope all across the world and these antimalarial drugs start to be vanished from the markets. Hopes become so much heightened that an event of severe toxicity reported by the national health officials of Nigeria when three people hospitalized due to overdose of these antimalarial drugs [25].

Now the question is either to use Chloroquine and Hydroxychloroquine for the prevention and treatment of COVID-19 or not. From medical science and patient's safety point, the answer is 'no' because these drugs have not been granted approval/licensed for use in treating the viral infections even. Other school of thought is that if there are no vaccines or therapeutic drugs exist for the treatment of COVID-19, what is the problem if Chlroquine/Hydroxychloroquine may be given to the COVID-19 patients. This point

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of view can be given weightage by assessing ratio of benefits and the side effects of these drugs. Most important is timing and stage of COVID 19 patient and duration of medicine to tackle side effects and to observe efficacy of Chlorquine.

Side effects of Chloroquine and Hydroxychloroquine

There has been published huge literature regarding side effects of these two drugs when used for treatment of malaria and rheumatic diseases. The Mayoclinic, CDC, WHO drug repository, Medline Plus and leading pharmaceutical companies have documented the side effects of using chloroquine and hydroxychroquine. Some of the consensus side effects are severe GI disturbances, neurological symptoms, visual and hearing problems, myopathies, dermatologogical pathologies and speech difficulties [26-30]. Here a very famous Danish study can be presented regarding the side effects of Chloroquine. They interviewed 4158 individuals through questionnaires. Their findings regarding severity of symptoms are given in the following table [31].

Table 1: Severity of symptoms due to prophylactic use of Chloroquine

Sr. No.	Complaints	Frequency (%)
1	No Complaints	85.5
2	Mild symptoms	11.1
3	Severe symptoms	1.5
4	Unacceptable	0.6
5	Terminated prophylaxis due to suspected side effects	2.8

Benefits may outreach the hazards

Now the question arises "Whether the benefits of using Chloroquine/hydroxychloroquine outreach the hazards". In view of above discussion, our answer is 'yes'. What rule we had set above is that risks and goods of the medicine must be compared and weighed when deciding to use a medicine or not. In present scenario and challenging situation of COVID-19 outbreak all across the world, when no prophylactic vaccines and antiviral drugs are available yet, there may be a room to add Chloroquine/Hydroxychloroquine as a potential supportive/therapeutic drug. Finally, results of another in vitro study are presented here in support of chloroquine use in treating the COVID-19 patients. The

authors of that study have reported that Chloroquine has potently blocked the virus infection at a very low –micromolar concentration in vitro on clinical isolates of COVID-19 patients and also in Vero cells infected with Novel Corona virus. Based on their in vitro findings, authors have suggested that Chloroquine should be assessed in human COVID-19 patients [32]. Chloroquine, a time tested antimalarial drug, has been reported to have broad spectrum antiviral effects. It also augments the immune system due to its immune modulating activity. When taken orally, chloroquine is distributed throughout the body organs, with maximum concentration in lungs [33-35].

Conclusion/Recommendations

Due to day by day worsening situation of Novel Corona virus outbreak all across the world, some immediate decisions must be taken. A team of experts and health authorities from all across the world must be sit together and should build consensus whether to use Chloroquine/Hydroxychloroquine in treating the COVID-19 patients or not. This team must also decide about the prophylactic use of these drugs in general public. Although this is an era of biotechnology, still it will take many months to years for the development of prophylactic vaccines and therapeutic antiviral drugs. During this lag period, Chloroquine/hydroxychloroquine may be proven a cheap, safe and effective option, but it must be administered in hospital settings under supervision of panel of physicians to control any untoward happening timely.

Conflict of interest

"The authors declare(s) that there is no conflict of interest regarding the publication of this paper**"**

Data availability statement

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Author's contribution

All the authors have contributed equally

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