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Chloroquine and Hydroxychloroquine for the Prevention and Treatment of COVID-19: A Fiction, Hope or Hype?

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ABSTRACT

Background: Curative part is one of the most important part of the COVID-19 containment strategy and various drugs are bring repurpose to treat the COVID-19 symptoms as there is no already available standard course of treatment due to novelty of the disease.

Summary: HCQ and CQ have showed their efficacy as antimalarial drugs both in prophylactic role and during treatment of the malaria. The initial studies which showed the successful lowering of viral load and lung injury along with reduced hospital say prompted health care professional all across the globe to widely administer the drugs in almost all patient. But soon, health acre fraternity realized that the drug is not suitable for all section of patient and is creating side effects which are life threatening in nature. In many cases the drugs were found to be effective in inhibiting the virus. Such drug has long list and contain chloroquine and hydroxychloroquine.

Conclusion: Several studies depicting the efficacy of the HCQ and CQ are quite promising and it has also proved to be game changer in many of the cases changing the course of infection in favour of the infected patients. But several concerns which are genuine in nature must be addressed in order to devise a fool proof strategy to curb the spread of COVID-19. Although the drug has shown some negative effects and proven in efficient in some cases, complete denial of the drug is not the option as we should not forget to try every option available to control the pandemic a soon as possible. More study which can highlight the group between the drug is safe should be done to demystify the facts.

Key words: COVID-19, Chloroquine, Hydroxychloroquine, Immunosuppressant, Cytokine storm, Combination drug

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INTRODUCTION

Coronavirus disease 2019 or COVID-19 has started its unfortunate journey in last part of the 2019 and still it is conditioning its fatal existence. It is mainly caused by the novel Coronavirus or newest entrant in the *Coronaviridae* family which resembles to the shape of the crown hence named novel Coronavirus. The novel Coronavirus is extremely contagious and it took less than a month to spread all over the world. The patient zero who is the first patient of the COVID-19 who died of the pneumonia supposedly was the victim of the spill over effect in which the virus got transferred to humans from bats that are infamous for harbouring lots of viruses *via* pangolin. Till now December 13, 2021, 270,405,290 infection cases has been registered which is unprecedented and 5,309,295 case mortalities has been registered indicating the ability of the virus to create such medical complications that spirals to the fatal clinical outcome [1]. The treatment of the disease is the crucial aspect in containing the disease spread and it includes clinical interventions. Several drugs which were already in use were repurposed to treat the symptoms of COVID-19 [2]. In many cases the drugs were found to be effective in inhibiting the virus. Such drug has long list and contain chloroquine and hydroxychloroquine [3]. Both the drugs were extremely popular among the health care professionals after several promising results came out from various studies across the world researching on the efficacy of the drug. But some side effects and in efficacy reports were also registered indicating relying on one single drug is not a good strategy. These drugs have a long history of being used as antimalarial drug and proved efficient there [4].

LITERATURE REVIEW

Pathophysiology of COVID-19

More than five million people suffered the death blow from the disease named COVID-19. It is considered as one of the deadliest event in human history as no other event

was successful in taking such huge toll on people's lives. The COVID-19 which is an acronym for Coronavirus disease 2019 is caused by the member of notorious virus family named *Coronaviridae*. The name of the virus is novel Coronavirus which has joined the long lineage of the human Coronaviruses [5]. There are in total 29 human Coronaviruses identified and seven of them had earlier caused some serious outbreaks. Novel Coronavirus belongs to this group and so far has shown most destructive behaviour among all of them. Novel Coronavirus is a beta Coronavirus and primarily affects the pulmonary organs system as it is the first in line of all the system. The novel Coronavirus is spread through droplets and discharges from infected person and enters the person's body through nose, mouth and eyes. Then the viral load stats to go towards lungs and starts to multiply. The Angiotensin Converting Enzyme 2 (ACE-2) receptors are resent all over the vital organs systems including lungs, heart, liver, kidney etc. and act as gateway for the virus to enter the host cell. Also viruses are considered as half living organism as they need a host to multiply and proliferate otherwise they remain inactive. Novel Coronavirus spread to every part of the globe. Even the remotest tribes of the world that are living almost in isolation got infected with the virus. There are two main reasons behind such happenings [6]. First that the virus is highly infectious and transmissible meaning it can quickly infect multiple people if only on infected individual came in contact with them. Second, viruses have the ability to exploits the lacunae in immune system and create unmanageable medical complications. These two capabilities make it one of the most destructive viruses the world has ever seen. The ACE-2 receptors present on the alveolar tissues makes the lung more prone to injury as ACE-2 is the facilitator for the virus to enter the cell. Virus then absorbs all the nutrients and disturbs all the cellular function. All the protein synthesis which is essential for the human anatomical function is stopped and virus takes complete control of the cell. After complete absorption from the cell, the cell then bursts resulting into more proliferation of the virus surrounding area. The virus then rapidly transgressed to other organs and organs system *via* blood and infiltrates the organs at cellular level affecting the functioning of the organ. The symptoms of the disease have wide spectrum of types in it and are categorized as mild, moderate, severe, critical symptoms [7]. Mild symptoms are cough, cold and minor fever along with fatigue. These are most common of the symptoms and can be seen in the entire geographical region and all the types of patients. These categories of patients may not need hospitalization and can be easily treated at home provided a burse or health care professionals is constantly available at the call as the viral behaviour is extremely unpredictable. Basic medication course along with proper rest and diet can cure these types of patient. Although not all patient of this category show such behaviours and consultation with health care professionals at every stage is extremely important. The moderate symptoms can be treated at home but the supervision of the doctor along with more complex medications may be required. Also need for hospitalization may arise in the due course of treatment. Severely ill patients are compulsorily treated at dedicated COVID-19 care facility as they are difficult to manage clinically [8]. Constant monitoring of all vital parameters along with medicinal interventions is necessary. Various reports to check inner functioning of the body can be prescribed and hence they must stay at the hospital facility until completely ameliorated from the condition. Critically ill patients need sophisticated medical care such as intensive care unit, oxygen support system, mechanical ventilation, occasional surgical intervention in order to save the patient from the fatal clinical outcome. These patients contribute the most to the case fatalities as they often manifests complications created by novel Coronavirus which are difficult to deal. The novel Coronavirus has crated many types of complications among patients that makes even healthy person to experience severe symptoms.

Repurposing of the existing medications for treatment of COVID-19

The novel Coronavirus as the name suggests is the new entrant in the virus family named *Coronaviridae*. The disease caused by the new virus is also new to the world as world has never seen such disease before. All the pathophysiology and clinical manifestation of the disease is new and hence no precedent of the disease or records of patients available with the health acre authorities. Therefore a whole new and unique strategy is needed to contain the viral pandemic [4]. New methods and measure has to be device in order to successfully control the wrath of novel Coronavirus causing COVID-19. Health acre authorities and governments along with law enforcement agencies around the world came up with all new methods to arrest the spread of the novel Coronavirus. Various Non-Pharmacological Interventions (NPI's) was implemented worldwide in order to control the pandemic anyhow. These non-pharmacological interventions includes lockdown, movement restrictions, wearing of masks, maintain minimum physical distance of two meter, regular sanitation of hands, prohibition on touching public surfaces. All these measure have the component of isolating the people from virus [9]. These measures were effective to a certain degree but the virus spread to every nook and cranny anyhow. Therefore large number of people got infected with the virus and need of medical intervention arose. As earlier stated, there were no medical intervention already available, health care professional's starts to administer medication according to the symptoms shown by the patient and its clinical history. The administration of ad hoc and top health care authorities has relied upon the wisdom and experience of the medical officer in charge of the COVID-19 care facility in selecting medications, especially for the severely ill patients. Initially symptoms like fever, cough and cold was treated with the regular antibiotic medication and patients were responsive to the medications hence it was continued. As the time passed several observations and studied published suggesting the efficacy and inefficacy of the drugs being administer all round the world. It

acted as a guide for the local health care professionals to effective treat and rectifies their medicine administration methods. Various studies around the world suggested some lifesaving medications which can lower down the case fatalities as these were proven to be efficient among small groups and were ready to be implemented on large scale patients. These lists of medications which were suggested to be administering on severely ill patients contain chloroquine and hydroxychloroquine.

DISCUSSION

Chloroquine and hydroxychloroquine in COVID-19

There are the drugs which were extremely popular and their demand sky rocketed every part of the world. CQ and HCQ are used to treat malaria and also to prevent it and is basically antimalarial drug. The discovery of the drugs is age old. In fact they were given as prophylactics to the soldiers battling for their respective country in Second World War as the war condition mandates taking some. CQ is used where HCQ cross reacts and HCQ is administered when CQ is inappropriate. HCQ contain one hydroxyl group extra as it eliminates the hazards caused by the CQ and considered a safer alternative [10]. These medications are used in certain autoimmune disorders like lupus erythematous, diseases like rheumatoid arthritis along with other different medications. Both of the medications are administered through oral route. World Health Organization has listed this medication as essential medications and it is also available in generic form. IT acts as first line drug for the treatment of the malaria. As the rheumatoid arthritis activates the immune system to greater extent and it does more harm than good, these medication known to have been suppressing immune system to control the inflammation in the body and joints become less painful. Both of the drugs, CQ and HCQ have mild side effects and which non-life threatening in most of the instances [11]. The side effects includes gastrointestinal disorders, pruritus, cutaneous manifestation which are uncommon and only 10% of the patent experience these symptoms. Chronic intake in high dosage can lead to neuro myopathy, retinopathy, cardio toxicity but it can easily controlled with dose regulation and lessening the amount over the course of treatment. It basically works by blocking the receptors of the innate immune system response which numbs down the response. It binds with some of the receptors and inhibits some of the enzyme so that over activation can be prohibited [12].

The pathophysiology of the COVID-19 is such that it develops itself to effect wide variety of the system inside of the body [13]. The cytokine storm which is the over activation of the immune system and in which there is over inflammation all over the body resulting into damaging of the tissues on the several vital organs like lungs and cardiovascular tissues. Cytokine storm is one of complicated manifestation of the COVID-19 which often leads to patient's fatal clinical outcome. Innate immune response of the body should be in healthy position so that any pathogenic external invasion can be dealt with utmost force and priority. In fact innate immune response plays a crucial role in deciding the patient's clinical outcome during the course of the COVID-19 infection. But sometime this innate immune response can overshoot its expectation and can prove fatal for the patient [14]. As the innate immune response detects the external pathogenic invasion, the response is activated and inflammation starts to arise. But if this inflammation is uncontrolled and all over the body then it is a serious cause of concern. Therefore extreme need of medicinal intervention arises as the patient can slip into pneumonia and lung injury. Lung is one of the most vital organs of the body as it provides other organs, oxygen, without which one cannot sustain the function of the body. Lack of oxygen can give rise to multi organs failure. Therefore it is important to control; the immunes system response and for that the method of immunosuppression is chosen in order to mellow down the immune system response which is killing healthy cells along with virus. Several medications are used as immunosuppressant and are quite popular among doctors and health care professionals while dealing with COVID-19 patients having severe symptoms like pneumonia. Therefore CQ and HCQ were among the top drugs that were prescribed to the severely ill patient as it was found to be lowering the inflammation load of the body along with the oxidative stress it is causing. Also the prior usage of the said drugs in SARS outbreak prompted the health care professionals to use the same in COVID-19 also due to its similarities with the prior one. The hype about the drug was so much so that the drug prices sky rocketed and hoarding of drugs stated which made the drug extremely expensive [15]. In fact relatives of the patients were travelling hundreds of kilo meters to buy CQ and HCQ for much more money.

Many health acre authorities tried it as the prophylactics to the health care workers as they were the front line workers and have the prime contact point with the infected patients. Back by ten the vaccine was also elusive and there was considerable amount of time to get approved the vaccine candidate as the arduous process of phase wise trials was remaining. Therefore to assess the efficacy of the HCQ, it was prescribes as prophylactic to HCW. A study done on the drugs suggests that both of the drugs are effective in entry level as well as post entry level of the novel Coronavirus causing COVID-19. In the comparative study of the both the drugs HCQ fond to have more impact as treatment drugs as well as prophylactic drug than CQ as showed in *in vitro* study. Another study conducted in china among the 100 patients of COVID-19 showed the drug's efficacy in inhibiting the exacerbation of the COVID-19 pneumonia and controlling it, bettering the radiological examination results indicating the healing of lung damage and the hospital stay was shortened after the administration of drugs [16]. As the health care facilities across the world are reeling under huge pressure of the influx of patients of COVID-19 and especially the sophisticated health care facilities and equipment's are already lacking, this quality of the drugs was nothing less than panacea and health care professionals started to prescribe it after seeing

such promising results of the study conducted on the efficacy of the drugs in COVID-19. Also another study conducted on 20 patients group who were suffering from novel Coronavirus causing COVID-19 which were administered HCQ. On third, fourth and fifth day the viral load among the patient was dropping who had upper and lower respiratory tract infection and patients were easing up to the condition. This section of the patients was highly vulnerable having high mean age and comorbidities. These promising results further prompted the usage. On sixth day up to 70% reduction in their viral load was shown giving hopes for many severely ill patients. Dual treatment drug that is CQ and HCQ showed 100% success rate while HCQ single headedly lowered down the viral load by 70% [17].

Although all is not good when it comes to administration of HCQ and CQ to all patients. Some of the studies also showed some negative impact also known as side effects of the drugs which are quite prominent. The combination of HCQ and azithromycin was administered on patients group having mean age of 58.7 years and having multi pole comorbidities like obesity, cancer and HIV. The result of these studies was one patent died even after administering the said dual drugs and 2 of the patients group was shifted to intensive care unit, remaining seeing negligible to no decrease in their viral load and the condition of the patients was not improving even after the administration of the drugs. A retrospective analysis of 181 patients from France of which 84 received the dosage of HCQ in the pattern of 600 mg per day and rest of the patients did not receive [18]. No difference was observed after seven days among both section of the patient and HCQ was stopped as prescribed medications as patients who were administered HCQ were showing abnormal electrocardiogram readings. In another study conducted on 84 patients in Unites States of America suggested increased cardiovascular risk. The combination of HCQ and azithromycin was given to the patient and 30% of the patients showed elongation in QT response interval. The renal failure was outcome among some the patients having comorbidities. A multinational study underlines the risk of developing angina, chest pain, risk of heart failure and other cardiovascular ailments. Various other studies highlighted the inefficacy of the drugs and the course of medications modified according and alternate existing medication was brought into the list of medications that can be administered to the patients of COVID-19 [19].

CONCLUSION

Several studies depicting the efficacy of the HCQ and CQ are quite promising and it has also proved to be game changer in many of the cases changing the course of infection in favour of the infected patients. But several concerns which are genuine in nature must be addressed in order to devise a fool proof strategy to curb the spread of COVID-19. Various studies depicting the inefficacy and rather side effects inducing quality of HCQ and CQ must be carefully examined ad side effects could culminate into life threatening condition for the patients. Especially comorbid patients where their condition of the patient is already not good and side effect can exacerbate the severity of the COVID-19. The hype of any drug is unjustified as it creates more demand which is impossible to meet especially when there is little evidence backing the efficacy of the drugs. Mere hype should not guide the treatment strategy as relatives are distress already and they are fighting their nest to save their patient. Alternative drugs having similar soothing effects rather more efficient must be searched for in order to lower their dependency over one particularly drug be it HCQ, CQ or any other drug. The rush for CQ and HCQ is unjustified and therefore should be stopped. Its usage as prophylactics also must be stopped as several side effects have been seen especially among elderlies and comorbid patients.

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