Medicine & Clinical Science

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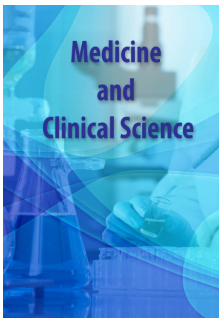

Repurposing quinine for severe COVID-19 – A preliminary study

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Abstract

LiveWell Initiative LWI, a self funded nonprofit social enterprise (www.livewellng.org) has, for 5 years, supervised MPH and DrPH Practicums for the Harvard T. H. Chan School of Public Health, Harvard University, Boston USA. It also supervises PhD thesis at University of Helsinki, Finland. The organization has repurposed quinine for use in moderate to severe coronavirus disease (COVID-19) by compiling three sets of STUDY PROTOCOLS in response to the COVID-19 RESPONSE with a goal to arriving at a practical and affordable solution to the pandemic. The protocols underwent debates and hypothesis testing among physicians, researchers, pharmacists and virologists. The protocols, still undergoing random Physician–Patient Trials at the discretion of prescribing clinicians and clinical researchers, are as recommended in a compilation of recent findings by LiveWell Initiative LWI on COVID-19. It is a study protocol designed to 'evolve' as a solution to COVID-19 response.

The protocols strongly suggest the use of quinine for COVID-19 treatment in moderate to advanced disease, recommending intravenous infusion of quinine for critical care in COVID-19. The sample size in a preliminary study, though small, points at quinine for severe COVID-19. Further studies are recommended but the result of this preliminary study is significant. The preliminary results were positive, and were posted online even as the concurrent study continues.

The 4-aminoquinolines have the same characteristic effects on the coronavirus, and quinine is the potential COVID-19 eradication tool.

In conclusion, quinine is impactful with positive outcomes for severe or advanced COVID-19 especially after the cytokine storm, with 5-7 days total recovery after the onset of the cytokine storm. Due to small preliminary sample size with 100% positive outcome, a full study should be commissioned to establish and quantify the impact of quinine on thousands in a population. This will help to prevent further morbidity in COVID-19 and the cytokine storm will be greatly overcome.

Introduction

A Coronavirus is an enveloped, positive single-strand RNA virus which belongs to the Orthocoronavirinae subfamily, as the name, with characteristic "crown-like" spikes on their surfaces, thus the word corona [1].

Chan, J et al. (2020) stated that alongside SARS-CoV, bat SARS-like CoV and others, it also fall into the genus beta-coronavirus (1,2). COVID-19 (caused by 2019-nCoV infection) is classified as a fifth-category notifiable communicable disease in Taiwan on January 15, 2019 [3].12 The genus beta-coronavirus can be divided into several subgroups. The 2019-nCoV, SARS-CoV, and bat SARS-like CoV belong to Sarbecovirus,

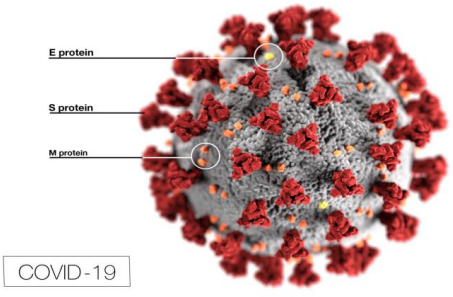

Figure 1. *SARS-CoV-2 (virus)*

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while the MERS-CoV to Merbecovirus [4].13 SARS-CoV, MERS-CoV, and 2019-nCoV all cause diseases in humans but each subgroup may have mild diverse biologic characteristic and virulence [5-7].9–11

The actual origin, location, and natural reservoir of the 2019-nCoV remain unclear, although it is believed that the virus is zoonotic and bats may be the culprits because of sequence identity to the bat-CoV [5]. According to previous studies on the SARS- and MERS-CoV, epidemiologic investigations, their natural reservoir is bat, while palm civet or raccoon dog may be the intermediate (or susceptible) host for SARS-CoV and the dromedary camel for MERS-CoV [5]. A field study for the SARS-CoV on palm civet ruled out the possibility as the natural reservoir (low positive rate); instead, the prevalence of bat coronavirus among wild life is high and it shares a certain sequence identity with the human SARS-CoV. Therefore, bats are considered the natural host reservoir of SARS-like coronavirus. However, the origin or natural host for the 2019-nCoV is not clear, although it might come from a kind of wild life in the wet market. Theoretically, if people contact or eat the reservoir or infected animal, they could be infected. However, to result in large scaled person-to-person transmission as in the past SARS outbreak, the virus must spread efficiently.

COVID-19 can affect any age group. Most of the cases (77.8%) were in 30-69 years age group. Pre-existing hypertension, diabetes, cardiovascular, cancer, and chronic respiratory illness are at risk of complications with a little male predominance (51.4%).

Initially, the 2019-CoV outbreak was reported as limited person-to-person transmission and a contaminated source from infected or sick wild animals in the wet market may have been the common origin (1,2). But more and more evidences came out with clusters of outbreaks among family confirmed the possibility of person-to-person transmission [3]. Furthermore, the presence of human angiotensin-converting enzyme 2 (hACE2) as the cellular receptor (like SARS) made droplet transmission to the lower respiratory tract possible [8]. Furthermore, it is similar to contact transmission like SARS, although the survival time in the environment for the 2019-nCoV is not clear at present. Currently, there was no evidence of air-borne transmission.

Viral RNAs could be found in nasal discharge, sputum, and sometimes blood or feces [8]. However, oral-fecal transmission has not yet been confirmed. Once people are infected by the 2019-nCoV, it is believed that, like SARS, there is no infectivity until the onset of symptoms. The exact survival of it in the environment is unknown; however in Africa it is believed that the virus is not spreading as much as it should due to the high numbers of BCG Vaccinated Africans [9,10]. This is not however not proven. Though considering characteristics of SARS-CoV and MERS-CoV, it may survive on a surface for hours to days at room temperature (average 20°C) and with high humidity. It can be killed by soap wash and disinfectants such as 75% alcohol. The incubation period is two days to 14 days. Initially, asymptomatic carriers were thought to be non-contagious. Later on in China, a cluster of cases in a family was reported to be contracted from an asymptomatic carrier who recently traveled from Wuhan. The infectious doses for 2019-nCoV is not clear, but a high viral load of up to 108 copies/mL in patient's sputum has been reported. The viral load increases initially and still can be detected 12 days after onset of symptoms. Therefore, the infectivity of patients with 2019-nCoV may last for about 2 weeks. However, whether infectious viral particles from patients do exist at the later stage requires validation.

The cytokine storm and COVID-19

The immune system protects us from microbes such as bacteria or viruses, when they invade the body. A host of specialized white blood cells that make up the immune system usually seek to identify pathogens and destroy them. When these pathogens are identified, the immune cells need to respond in defence and recruit more immune cell thus signalling to the cytokines.

Once released, the cytokines stimulate localized inflammation. This is a physiological response by the body which aims at destroying the pathogen. Notable signs of inflammation include redness, pain, swelling, and elevated temperature.

Cytokines released, work by binding to receptors found either on nearby cells or even on the same cell that released them. Some cytokines can stimulate further release of cytokines, creating a positive feedback loop and amplifying the inflammation. Often this results in fever, a key hallmark of inflammation.

Sometimes, the immune system overreacts during an infection, releasing more cytokines than required, hence, recruiting new hordes of activated "angry" white blood cells, which produce even more cytokines. This means a "cytokine storm" is emerging.

COVID-19 treatment with quinine

As of present, there is yet to be an ideal treatment for COVID-19, the treatment is mainly supportive. All patients should be treated in the hospital. However, due to a shortage of beds and resources, uncomplicated mild cases may be treated at home isolation with minimum contact of a few caregivers preferably one-on-one with the practice of hand hygiene and using of masks. The caregiver should be a healthy individual without any immune-suppression. The room should be well ventilated with windows open. A minimum of one-meter space should be maintained.

Why quinine?

Quinine a senior counterpart 4-aminoquinoine, holds sway in the treatment of COVID-19.

It is a repurposed drug with unique strengths 37.

All the Aminoquinolines have unique properties against COVID-19 namely:

- Antiinflammatory
- Antiviral
- Antiprotozoal
- Antiparasitic
- Haemozoin Inhibitors
- Zinc Ionophore
- PCR Inhibitor

In addition, Quinine crosses the blood-brain barrier BBB, and it will therefore cross into the membranous alveoli in COVID-19 and clear out the viruses in situ.

Repurposing the aminoquinolines

The process of 'repurposing', is receiving growing attention. This involves finding new therapeutic indications for old or currently used drugs such as Quinine, with an original indication to cure malaria, have now been successfully used to treat several other infectious diseases.

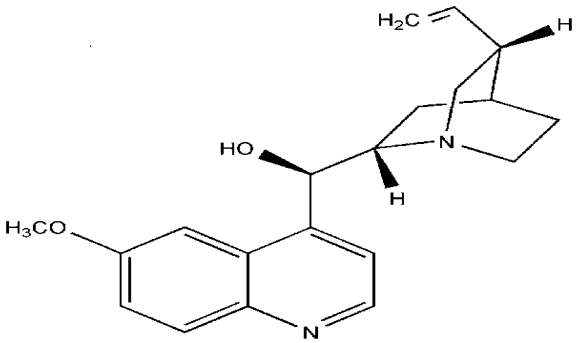
Indeed, they have anti-inflammatory, immunomodulating, anti-infective, antithrombotic, and metabolic effects. Among the biological effects of Quinine, it is important to highlight their strong antiproliferative, antimutagenic, and inhibiting autophagy capacities.

PROGNOSIS

Prognosis is good, especially no death occurred except in critically ill. It took about 5-8 days on average for recovery. Prior to discharging a patient during recovery case, two respiratory samples should be taken 24 hours apart and must be negative.

Recently few confirmed COVID-19 cases (HCWs) tested negative by rRT-PCR after hospital discharge. They were tested negative after 5 - 13 days of discharge during the home quarantine. They were asymptomatic and chest CT did not show any change from previous images.

Structure of quinine



Mechanism of action – Quinine

- Quinine has a multiple modes of action on the virus
- It prevents the virus from penetrating the host cell using its S protein and Protease
- It breaks the polymerase chain and prevents viral replication
- It is a zinc ionophore and ensures penetration of zinc into the viral cell, altering the pH
- Zinc also potentiates Quinine action, and Quinine has a good safety profile in therapeutic doses, with self limiting ototoxicity which is reversible upon completion of the regimen
- Suppress exagerrated Immunoglobulin response IgG and IgM through Immunomodulation and therefore also exerts
- Anti-inflammatory action
- A highly soluble and more potent 8-Aminoquinoline, Quinine, will cross the BBB
- Will therefore penetrate the Alveoli and displace the viruses, disseminate the glass ground opacity, restore heme iron and normalcy
- Haemozoin Inhibitor – starves the virus of its food vacoules
- In addition, Quinine is a muscle relaxant and a non-narcotic analgesic, taking care of the accompanying severe myalgia which characterizes n severe COVID-19

Categorisation of quinine use in COVID-19:

- **Moderate COVID-19** – Symptomatic, Laboratory Tested Positive COVID-19 Patient on admission at Isolation Center / Oxygen saturation between 90-94 – Oral Quinine Sulphate, 600mg t.i.d. for 5 days
- **Severe COVID-19** - Symptomatic, Laboratory Tested Positive COVID-19 Patient on admission at Isolation Center / Oxygen saturation below 90 – Intravenous Quinine Infusion, dose-determined by physician
- **Acute Severe COVID-19** - ICU Patient - Symptomatic, Laboratory Tested Positive COVID-19 Patient on admission at Isolation Center / Oxygen saturation below 80 – Intravenous Quinine Infusion, dose-determined by physician
- **Recommended Doose:** Quinine 600mg tds p.o. ot 600mg prn (Intravenous, administered in dextrose) as determined by the prescribing physician.
- Administration of anti-inflammatory, anticoagulant, antiibiotic and bronchodilator medications are an essential additive component of care in Severe COVID-19 Patients. Please refer to LWI Study Protocols.

Affordable, replicable, scalable

- The remedy is affordable, scalable and replicable for all low-income economies.
- It is hereby strongly recommended for use everywhere in the world.

Preliminary data

Study Protocol	Frequency
Inpatient	11
Outpatient	1
PEP	34
PrEP	76
ICU_Patient (Treated on Quinine i.v.)	1
Grand Total	123

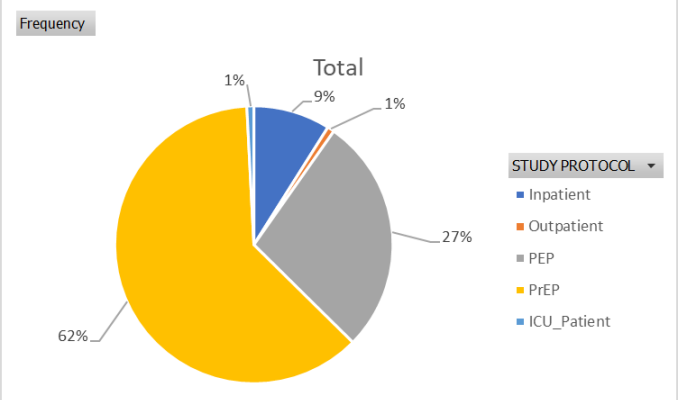


Table 1. Designation of respondents

Discussion

The results in this preliminary study are based on preliminary data gathered from physician-patient recommendations of prophylaxis using the 4-aminoquinolines in COVID-19 Treatment and prophylaxis. It also recognises some self-medicating individuals who took advantage of the non-prescription remedy.

The LWI study protocols are currently being used in Kaduna State, Bauchi State, and some other States in Nigeria. The unique thing about the study protocols, the 4-aminoquinolines offer an end to end care in COVID-19, from CQ/HCQ in pre and post exposure to mild and moderate COVID-19 and escalating into quinine I.V. for critical care in COVID-19.

Quinine works in advanced COVID-19 as the single laboratory tested positive client on the ventilator, has fully recovered after treatment with I.V. quinine and is still symptom-free 6 weeks post-lockdown.

Conclusion

The re-purposing of quinine, sets the benchmark for the management of moderate to severe COVID-19, and therefore completes the treatment curve for COVID-19 in today's modern scientific world. Quinine is very strongly recommended for COVID-19 Treatment, to reverse the pandemic..

Conflict of interest

The authors declare that there are no conflicts of interest.

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