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Research Article

THERAPEUTIC EFFICACY OF HYDROXYCHLORQUINE IN COVID-19: A SYSTEMATIC APPROACH

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A B S T R A C T

Corona virus induced disease, COVID 19 is a rapidly emerged and wide spread infection throughout the world. The disease does not have any proven medications or protocol. Therefore several medicines were trailing and hydroxychlorquine and a combination HCQ with azithromycin earned a special attention among them. The clinicians started to prescribe the patient with HCQ and combination and started reporting the clinical effects. This a small narrative review regarding the effectiveness' of HCQ and combination in the reduction of viral load in COVID patients.

INTRODUCTION

Coronavirus induced disease 19 COVID-19 is an infectious disease caused by corona virus. It is officially known as severe acute respiratory syndrome coronavirus 2. Mild to moderate respiratory illness will occur in most infected persons with virus infection and in most cases, recovery is possible without any special treatment. But high risk is observed among aged and Co-Morbid patients and the infection can be severe which may even lead to death (Alhazzani W *et. al* 2020) (Chen Net. al 2020) (WHO Coronavirus disease 2020)

Due to the rapid transmission rate and severity, the world health organization (WHO) declared it as a pandemic. The virus materialized in Wuhan, Hubei province, China and spread throughout the world. (Organization WHO 2020) The proper protocol or treatment is not available for this disease and no drugs were approved for the same. But countries and provinces are making their own guidelines to treat COVID- 19. So many drugs are being tried for cure and also under trials. The latest news and studies reveal that an age old anti-malarial drug hydroxychlorquine (HCQ) is effective in COVID 19 for reduction of viral load and clinical betterment. The HCQ's unindicated use can lead to severe unintended reactions and may even lead to death. In this present attempt, we are aiming to converge evidence from available original research articles to analyse the efficacy of HCQ.

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MATERIALS AND METHODS

Electronic database PubMed was systematically searched for articles using the keywords hydroxychlorquine, coronavirus and COVID-19 up till April 14 2020. A total of 67 articles regarding these keywords were found. After excluding all studies other than original research with clinical study and full-text availability a total of 6 were obtained. There were 2 Chinese study which was eliminated due language issue and finally we analysed 4 studies. It includes one study each from a non-randomised clinical trial, randomised clinical trial, and pilot observational study.

The analysis includes 4 studies, in each study, we have taken name of author's, publication year, sample size, participant' sage, and trail design, duration of follow-up, description, dosage, outcome and major findings.

RESULTS

Enrolled studies The selected studies are summarized in table1 Gautret.P *et. al* ; 2020 conducted an open-label non randomised clinical trial at south France to identify the role of HCQ in reduction of respiratory viral load in COVID-19 positive patients. The test arm contained patients willing to undergo the treatment protocol while those who refused were put in the control arm. A total of 36 out of 42 positive patients were included in the studyie; 20 persons in the test and 16 in the control. In the test, 2 treatment arms are used. For 14/20 patient were administered HCQ monotherapy (200mg TID) and 6/20 were given HCQ+ azithromycin combination therapy (500 mg1st day followed by 250 mg till 4th day). The primary outcome was viral clearance in the post 6th day. The viral

clearance was declared by PCR of the nasopharyngeal swab. Patients were classified as asymptomatic, lower and upper respiratory infection. The population had a mean age of 51.2 ± 18.7 for test and 37.3 ± 24.0 for control. The results say that 50% of patients in test arm convert to negative on day 3 post inclusion, when compared to 6.3 % in control with a p-value of 0.005. At day 6th post inclusion a total 70% patients turned to negative in the test arm, but only a 12.5 % converted to negative in control with p-value 0.001. The patients who received HCQ monotherapy had 35.7% conversion to negative on day 3 post inclusion and 57.1% conversion in day 6 post inclusion, while combining with azithromycin 83.3% conversion to negative occurred on day 3 post inclusion and 100% conversion in day 6 post inclusion. From the result, they concluded that HCQ is effective in reducing viral load and will be more effective in combination with azithromycin. (Gautret.P et. al 2020)

Chen.Z et.al; 2020 conducted a randomized clinical trial from February 4-28, 2020 in Renmin Hospital of Wuhan University. A total of 62 patients were randomized and included and randomized in a parallel group of 31 each. The study was done according to the standard research principles. The standard treatment was oxygen therapy, antivirals, immunoglobulin with or without corticosteroid which is given to control group and the same with HCQ in a dose of 200mg BD was given to the test. 5 days post enrolment or emergence of serious adverse event were the ends points of this study. For all patients, the mean age was 44.7 (15.3) years old and about 46.8% of the enrolled patients were males and 53.2% were females. It was observed that the condition of about 80.6 % (25/31) of enrolled patients in the test group improved compared to only 54.8% (17/31) in the control group. It was also noted that the exacerbation rate of control is 5 times greater than HCQ group. Also no ADR was reported in control group while test group reported 6.4% ADR. A 12.9% of patients in control group were progressed to severe illness and there were none in HCQ group. From the result, they partially confirmed that HCQ can be used for COVID, where there is no better option. (Chen.Z *et.al* 2020)

Gautret .P *et al* 2020 conducted a study to find out the clinical and microbiological need of an effective treatment to cure COVID-19. The study was conducted at the University Hospital Institute Méditerranée Infection in Marseille, France. A pilot observational method was chosen with sample size of 80 patients. There was 3 main outcomes and one among the three was to rule out the load of virus in the patient who treated with HCQ. A combination of hydroxychloroquine and azithromycin for at least a period of three days with 200mg TID HCQ and Azithromycin 500 mg in day 1 and 250 mg till day 4 were used. The study was conducted between 3rd March and 21 march 2020. The median age of patients involved were 52 years with a M/F sex ratio of 1:1. The duration of treatment was at least 3 days and follow up to 6 days. 81.3% of patient discharged in day 7. A total of 97.5% were found to negative on nasopharyngeal sample in day 5, Some of them shifted to ICU Reported ADR were minor and a total of 7 found. The result confirmed findings of the previous study by the same authors that the azithromycin and HCQ can reduce the viral load.(Gautret .P *et al* 2020)

Molina *et.al*; conducted a prospective study regarding the virologic and clinical outcomes of COVID patients with HCQ treatment. A total of 11 patients were enrolled in the study. 200 mg of HCQ was given for 10 days in a frequency of thrice a day and azithromycin 500 mg loading dose and 250 mg for next 4 days. The mean age of patients was 58.7 years old in which 7 were male. Among them 8 of them had comorbidities. After the period of 5-6 days, 8/10 patients were found to be positive on nasopharyngeal swab test and this study reveals that HCQ combination may not be as effective as proposed by other studies.(Molina *et.al* 2020)

Table 1 Summary of all studies

Study name	Gautret.P et.al 2020	Chen.Z et.al 2020	Gautret .P *et al* 2020	Molina et. Al 2020
Study site	south France	Wuhan	France	France
Sample size	36	62	80	11
Method	open-label nRCT	RCT	Observational Study	prospective
Primary outcome	Viral load	Disease progression And viral load	Clinical recovery	Viral load
Control	16	31	NA	NA
Test	20	31	NA	NA
Treatment	HCQ 200 mg TID (14/20):HCQ+ azithromycin 500mg LD & 250 mg up to 4day (6/20)	HCQ 200mg BD	HCQ 200mg TID + azithromycin 500mg LD & 250 mg up to 4day	HCQ 200 mg TID (14/20):HCQ+ azithromycin 500mg LD & 250 mg up to 4day (6/20)
Duration	10 days	5 days	10 days	10 days
ADR	NA	2	7	1
Severe illness (C/T)	NA	4/0	3/0	1
Mortality	0	0	2	1
Treatment Effect (C/T)	12.5%/70%	54.8%/80.6%	81.3%	18.18%

DISCUSSION

In these original articles, the authors studied the efficacy and safety of Hydroxychloroquine monotherapy as well as its combination with azithromycin. The studies point out that hydroxychloroquine is highly effective in reducing the viral load when given in combination with azithromycin. Being similar to chloroquine expcet in the structure that a hydroxyl moiety is present in one terminal of HCQ, these drugs alter the PH of acidic intercellular organelles which is essential for viral membrane fusion. (Mauthe *et.al* M 2018) HCQ being more potent and safer than chloroquine it inhibits both the entry and transport of SARS-CoV-2.All studies classified patients based on the symptoms and other different classifications.
(Liu J *et.al* 2020).

All the studies were only conducted for a short period. During short period the exact picture of efficacy and safety cannot be guaranteed. Not only that the doses used is same to anti-malarial dose.

The progression of disease and severity in HCQ treated patients are is less because HCQ or other combined agents have the power to reduce the viral load and even helpful to cure the COVID-19. At present many trials regarding the use of HCQ and HCQ + azithromycin are ongoing. Many of the clinicians are using the same in the absence of a better option. One of the study says that the combination is not found to be effective. Maybe the reason can be the majority of the patients have comorbidy like cancer and HIV. When considering agents like this all aspects of the drug should be considered. Sometimes it can lead to severe adverse drug reactions and other events. All the studies are only focusing on the efficacy not giving importance to the kinetics, dynamics, and other parameters. The medical field is very happy in the efficacy of HCQ and combination of HCQ with azithromycin. Even if the clinical benefits are there in this small population a wider trial

is wanted to be finished for a well-detailed report. The above mentioned studies are only weak evidence which is accessible now.

CONCLUSION

Additional trials and studies, which involves higher number of population is needed to find out the efficacy and safety of the HCQ and combination. Not only for the effectiveness but also for treatment protocol.

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