International Journal of Medical and All Body Health Research

International Journal of Medical and all body Health Research
ISSN: 2582-8940
Received: 14-04-2020; Accepted: 30-04-2020
www.allmedicaljournal.com
Volume 1; Issue 2; April-June 2020; Page No. 15-18

King Salman Specialist Hospital study for use of hydroxychloroquine in COVID 19 positive patients at Hail region, and relation with cardiovascular risk factors

Vlachopoulou M [1], Chatzis G [2], Sulami A [3], Karish MA [4], Gawish AE [5], A Almofadhli AE [6], Alharbi AS [7], Alsairra MNS [8], Aljarbaa NK [9], Al Harbi MN [10], Almansori AND [11], Alnawmasi MON [12], Aldogeman RZM [13]
[2, 4, 6-13] Department of Internal Medicine, King Salman Specialist hospital, Hail, Saudi Arabia
[3, 5] University of Hail, Hail, Saudi Arabia
[1], Hail Cardiac Center, Hail, Saudi Arabia

Corresponding Author**: Vlachopoulou M**

Abstract

Introduction: Hydroxychloroquine (HCQ) is an antimalarial drug that received worldwide news and media attention in the treatment of patients with coronavirus disease 2019 (COVID19). This drug was used on the basis of its antimicrobial and antiviral properties despite lack of definite evidence of clinical efficacy. In this study, we aim to assess the efficacy and safety of using HCQ in treatment of patients with COVID-19 who were admitted in King Salman Specialist Hospital, at Hail, KSA.

Methods: We conducted a retrospective cohort study on a random sample of patients admitted with COVID-19 between 1 April and 31 July 2020. The study was conducted in King Salman Specialist Hospital, Hail, KSA. Data was extracted from the medical records. The primary endpoint was the requirement of noninvasive ventilation, intubation, or death. Secondary endpoint was length of hospitalization for survivors and readmissions. Three methods of analysis were used to control for confounding factors: logistic multivariate regression, propensity score adjusted regression, and matched propensity score analysis.

Results: A random sample of 753 patients were included, 348 of whom received HCQ (treatment group) and 405 did not receive it (control group). Our results showed that HCQ did have a significant effect on primary outcomes due to COVID-19 infection when compared to controls after adjusting (P = 0.011). Co-administration of aspirin and dexamethasone had also effect on primary outcomes (P = 0.011). Morbid Obesity was associated with increased risk of primary and secondary outcome (P = 0.005)
Hydroxochloroquine was not associated with QT prolongation or cardiac arrhythmia.

Conclusion: Our results showed some beneficial effect of using hydroxychloroquine on the outcome of patients with COVID-19, and also aspirin and dexamethasone. Obesity however, in combination with diabetes mellitus, is a significant cardiovascular risk in patients with COVID 19 infection

Keywords: Obesity, Aspirin, COVID-19, Efficacy, Hydroxychloroquine, Respiratory failure, Safety, SARS-CoV-2, Cardiovascular disease

Introduction

An outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing the coronavirus disease 2019 (COVID-19), started in December 2019. Almost a year later, we seem to be at the brink of an imminent second wave. Since it was declared a pandemic by the World Health Organization (WHO) in March 2020, it infected more than 153 million people and led to the death of 3.3 million others [1].

The absence of an effective treatment against severe acute respiratory syndrome coronavirus 2 (COVID 19) infection, other than vaccination, has led clinicians to redirect drugs that are known to be effective for other medical conditions to its treatment [2].

Among these repurposed therapeutic agents are the antimalarial drug chloroquine and its analogue hydroxychloroquine, which is used for the treatment of autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis.

These drugs have been shown in laboratory conditions to have properties as well as immunomodulatory effects. The combination of hydroxychloroquine with a second-generation macrolide, such as azithromycin (or clarithromycin), has also been advocated. Previous studies have shown that treatment with chloroquine, hydroxychloroquine, or either drug combined with a macrolide can have the cardiovascular adverse effect of prolongation of the QT interval, which could be a mechanism that predisposes to ventricular arrhythmias.

Several multicenter randomized controlled trials are underway, but there is a pressing need to provide accurate clinical guidance because the use of chloroquine or hydroxychloroquine along with macrolides is widespread, often with little regard for potential risk. The purpose of this study is to retrospectively analyze data from Hail region regarding the use of hydroxychloroquine in COVID 19 positive inpatients, and to evaluate relation between use of this medication, in combination with other therapeutic measures, and the presence of complications and side effects.

Methods

- **Data acquisition**

Data was acquired from the electronic file of the inpatients from Medical plus Health insights system of medical records., exported in Excel template. All data from Medical plus are standardized from the Saudi Central Board for Accreditation of Healthcare Institutes (CBAHI). Data was extracted manually and added to the excel data gathering template by the doctors included in the study.

- **Study design**

We included all patients hospitalized between April and July 2020 at King Salman Specialist and with PCR-confirmed COVID-19 infection, for whom a clinical outcome of either hospital discharge or death during hospitalization was recorded. A positive laboratory finding for SARS-CoV-2 was defined as a positive result on high-throughput sequencing or reverse transcription-quantitative PCR assay of nasal or pharyngeal swab specimens, and this finding was used for classifying a patient as positive for COVID-19. COVID-19 was diagnosed, at each site, on the basis of WHO guidance. Patients who did not have a record of testing in the database, or who had a negative test, were not included in the study. Only one positive test was necessary for the patient to be included in the analysis. Patients who received either hydroxychloroquine or a chloroquine analogue-based treatment (with or without a second-generation macrolide) were included in the treatment group. Patients who received treatment with these regimens starting more than 48 h after COVID-19 diagnosis were excluded. We will define two distinct groups, ventilated and non-ventilated patients, and we will divide to sub groups according to treatment. We will also compare use of hydroxychloroquine to standard treatment in patients.

- **Data collection**

Patient demographics, including age, body-mass index (BMI), sex, race or ethnicity, and epidemiological score were obtained. Underlying comorbidities (based on International Classification of Diseases, tenth revision, clinical modification codes) present in either the inpatient or outpatient electronic health record were collected, which included cardiovascular disease (including coronary artery disease, congestive heart failure, and history of a cardiac arrhythmia), current or previous history of smoking, history of hypertension, diabetes, hyperlipidemia, or chronic obstructive pulmonary disease (COPD), and presence of an immunosuppressed condition (steroid use, pre-existing immunological condition, or current chemotherapy in individuals with cancer). We collected data on use of medications at baseline, including cardiac and diabetes medication. Initial clinical findings, as shortness of breath, cough, fever, fatigue, diarrhea and anosmia – hyposmia will be gathered. The initiation of hydroxychloroquine during hospital admission was recorded, including the time of initiation. The use of second generation macrolides, specifically azithromycin and clarithromycin, was similarly recorded. ECG and cardio evaluation was recorded.
Initial radiological and lab findings was recorded.

- **Outcomes**

The primary outcome of interest will be the association between use of a treatment regimen containing chloroquine or hydroxychloroquine (with or without a second-generation macrolide) and aspirin when initiated early after COVID-19 diagnosis with the endpoint of requirement of noninvasive ventilation, intubation, or death. The secondary outcome of interest will be the association between these treatment regimens with endpoint length of hospitalization for survivors and readmissions. We will also analyze demographic data and correlation between comorbidities.

- **Statistical analysis**

We will use IBM SPSS Statistics free version for various descriptive and predictive analyses of data, such as those generated by the COVID-19 pandemic, as the tool is already used by WHO.
Three methods of analysis were used to control for confounding factors: logistic multivariate regression, propensity score adjusted regression, and matched propensity score analysis. The distribution of treatment groups was summarized. Bivariate associations between the treatment group and the measured patient characteristics were analyzed using chi-squared (v2) tests for categorical variables and t test for continuous variables. We also assessed endpoints and adverse events and their associations with the treatment group.

- **Compliance with Ethics**

All methods and retrospective analysis of data were approved by the Saudi Central Board for Accreditation of Healthcare Institutes (CBAHI), and carried out in accordance with the local guideline and ethical guidelines of the Declaration of Helsinki 1975.

Result

753 cases were included in the study, after exclusion of patients not meeting the criteria of study (ventilatory support or death was achieved within 1 day, transfer/discharge within1 day, received HCQ out of study baseline), and propensity matched analysis to balance the two groups and their characteristics. Out of the 753 patients affected with COVID-19 selected in this study, 348 patients received HCQ and 405 patients did not. Among the patients who received HCQ, the median time to start HCQ was 1 day from admission (IQR 0–2).
Patients' baseline characteristics (demographic and clinical) according to HCQ exposure are shown in Table 1
The HCQ-receiving patients were more likely to be symptomatic. Symptoms of fever, cough, body ache, nausea, and vomiting were more predominant in patients who received HCQ, as also chest radiography findings. The HCQ-receiving patients were also more severely ill on admission, as 77.4% received supplemental oxygen on admission (through nasal cannula, face mask, and nonrebreather mask).

Table 1: (patient demographics and clinical characteristics)

Factor	Control	HCQ
Number	405	348
Nationality (Saudi)	179 (44%)	152 (43%)
Gender (male)	291 (72%)	249 (71%)
Diabetes Mellitus (DM)	160 (39%)	139 (40%)
Chronic Heart Failure (CHF)	24 (7%)	17 (7%)
Chronic kidney disease (CKD)	20 (5%)	14 (5%)
Ischemic Heart disease (IHD)	46 (14%)	34(10%)
Chronic obstructive pulmonary disease (COPD)	40 (10%)	29 (9%)
Obesity (BMI>30)	142(35%)	122 (36%)
Smoker	5 (15)	5 (2%)
Fever on Admission	250 (62%)	285 (82%)
Chest X-ray (CXR) infiltrations in admission	248(61%)	288 (81%)
Low lymphocyte count on admission	248 (61%)	302 (88%)
Increased O2 on admission	298 (72%)	269 (77%)

Primary Outcome

During the period of their admission, patients who did not received HCQ were more likely to develop the composite outcome. There was a significant effect modification in patients with COVID-19 receiving HCQ and aspirin on admission. The difference between the two groups was significant across the different methods used to control confounders. The primary analysis using multivariate model adjusting for confounding variables showed an odds ratio of 1.43 with a 95% CI 0.85–2.37, P = 0.011

Morbid Obesity was associated with increased risk of primary and secondary outcome (P = 0.005) Hydroxochloroquine was not associated with QT prolongation or cardiac arrhythmia.

The mean length of stay of discharged patients in the study cohort was 20.0 days (± 5.54 days). The minimum stay was 2 days, and the maximum was 57. The difference was statistically significant in a two-sided t test (p<0.001).

Readmissions was not statistically significant in both groups. Results are summarized in Table 2, 3 and 4

Table 2: (Summarized results)

Factor	Control	HCQ
Number	405	348
Mortality	58 (14%)	14 (4%)
Intubation	67 (16%)	18 (5%)
ICU length of stay (median)	16 (± 5.25 days)	13 (± 5.11 days)
Length of stay (median)	24 (± 5.65 days)	17 (± 5.41 days)
Readmissions	20 (5%)	14 (4%)
QTc prolongation (>440 ms)	19 (5%)	14 (4%)

Table 3: (Summarized results with aspirin)

Factor	Control	HCQ + aspirin
Number	405	50
Mortality	58 (14%)	9 (5%)
Intubation	67 (16%)	4 (2%)
ICU length of stay (median)	16 (± 5.25 days)	13 (± 5.11 days)
Length of stay (median)	24 (7%)	17 (7%)
Readmissions	20 (5%)	0 (0%)

Table 4: (Summarized results with Morbid Obesity)

Factor	Control	BMI > 30
Number	489	264
Mortality	40 (8%)	32 (12%)
Intubation	46 (9%)	39(15%)
ICU length of stay (median)	11 (± 5.25 days)	18 (± 5.11 days)
Length of stay (median)	14 (± 5.65 days)	27 (± 5.41 days)
Readmissions	20 (4%)	14 (5%)

Discussion

The results of this study show that, for our studied sample and models used, HCQ had a mild significant effect on primary outcomes (requirement for ventilation or death) due to COVID-19 infection [3].

Analysis of the demographics of our studied sample showed that patients who received HCQ were significantly of older age, which could be associated with a more severe HCQ-requiring presentation.

Patients who received HCQ had a higher presentation of symptoms on admission and scored significantly higher on baseline clinical severity scale. Creatinine levels were significantly elevated amongst patients who received HCQ, indicating COVID-19-mediated acute kidney injury [4].

A significantly higher proportion of HCQ receiving patients presented with chest x-ray findings of pneumonia compared to control patients [5]. Patients in our study who received HCQ while on oxygen therapy had lower rates of developing the primary outcome. Our study showed mild clinical benefit from using HCQ in hospitalized patients with COVID-19. Moreover, the effect remained significant across different subgroups: room air/oxygen therapy and with and without aspirin and dexamethasone cotreatment [6].

Obesity, especially BMI >30, which is prevalent in Saudi Arabia and the region of Hail, showed to have lethal consequences in the COVID 19 inpatients, especially in the diabetes mellitus subgroup.

Our study showed that HCQ mildly affected the length of hospitalization. The raw analysis showed a significantly lower length of stay compared to patients not receiving HCQ, consistent with several reports [7, 8]. It will be expected that the more severe presentation, higher comorbidities, and risk of lower prognosis leading to the administration of HCQ to prolong the hospitalisation [9]. Hence, patients who received

HCQ would be expected to require a longer stay.

The surprising result was the insignificant association between QT interval prolongation and the use of HCQ. Most studies showed frequent prolongation of the QT segment [10]. Our result can be explained by the local protocol used in our hospital, as daily ECG was done for all patients on HCQ. The local protocol suggested withholding HCQ once QT exceed 440 ms and can then be restarted once QT has decreased. Moreover, patients with a baseline QT greater than 440 ms or those who are at risk for developing cardiac arrhythmia or QT prolongation were rarely prescribed HCQ.

The relevance of obesity in combination with diabetes mellitus as a significant cardiovascular risk in patients with COVID 19 infection may be of major concern with relevance to the use of HCQ. In the global chronic disease syndrome with obesity and diabetes the anti-aging gene may be repressed and the patients may be at risk for programmed cell death. The use of HCQ with relevance to anti-aging gene inactivation may result in poor study results in these COVID-19 patients [11].

Conclusion

Our results showed some beneficial effect of using hydroxychloroquine on the outcome of patients with COVID-19, and also aspirin and dexamethasone. Obesity however, in combination with diabetes mellitus, is a significant cardiovascular risk in patients with COVID 19 infection. However, this is not supported by other studies, specifically the RECOVERY trial, which randomized 4716 patients across 176 hospitals in the UK, showed that HCQ had no benefit in decreasing mortality nor invasive ventilation [12]. A very small number of studies supports improvement in mortality, wth the majority conclude to no benefit, or the opposite [13]. Also, we acknowledge the limitations of a retrospective study, both in volume aof the patients and credibility of results.

Still, it is a significant finding toward the benefit of the COVID 19 patient.

References

1. World Health Organization. WHO coronavirus disease (COVID-19) dashboard. WHO, 2020. https://covid19.who.int.Acceses on 10/5/2021
2. Principi N, Esposito S. Chloroquine or hydroxychloroquine for prophylaxis of COVID-19. Lancet Infect Dis 2020; published online April 17. https://doi.org/10.1016/S1473-3099(20)30296-6.
3. Perricone C, Triggianese P, Bartoloni E, *et al*. The anti-viral facet of anti-rheumatic drugs: lessons from COVID-19. J Autoimmun 2020. Published online April 17. DOI:10.1016/j.jaut.2020.102468.
4. Liu J, Cao R, Xu M, *et al*. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discov. 2020; 6:16.
5. Devaux CA, Rolain JM, Colson P, Raoult D. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? Int J Antimicrob Agents, 2020. Published online March 12. DOI:10.1016/j.ijantimicag.2020.105938.
6. Tang W, Cao Z, Han M, *et al*. Hydroxychloroquine in patients mainly with mild to moderate COVID-19: an open-label, randomized, controlled trial. Med Rxiv, 2020. Published online May 7. DOI:10.1101/2020.04.10.20060558 (preprint).
7. Chen J, Liu D, Liu L, *et al*. A pilot study of hydroxychloroquine in treatment of patients with moderate COVID-19. J Zhejiang Univ (Med Sci). 2020; 49:215-19.
8. Gautret P, Lagier JC, Parola P, *et al*. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents, 2020. Published online March 20. DOI:10.1016/j.ijantimicag.2020.105949.
9. Ray WA, Murray KT, Hall K, Arbogast PG, Stein CM. Azithromycin and the risk of cardiovascular death. N Engl J Med. 2012; 366:1881-90.
10. Giudicessi JR, Noseworthy PA, Friedman PA, Ackerman MJ. Urgent guidance for navigating and circumventing the QTc-prolonging and torsadogenic potential of possible pharmacotherapies for coronavirus disease 19 (COVID-19). Mayo Clin Proc, 2020. Published online April 7. DOI:10.1016/j. mayocp.2020.03.024.
11. Covid-19 Infection and Anti-Aging Gene Inactivation. Acta Scientific Nutritional Health 4.5, 2020, 01-02.
12. Horby P, Mafham M, Linsell L, *et al*. Effect of hydroxychloroquine in hospitalized patients with covid-19. N Engl J Med. 2020; 1:2.
13. Axfors C, Schmitt AM, Janiaud P, Van't Hooft J, Abd-Elsalam S, Abdo EF, *et al*. Mortality outcomes with hydroxychloroquine and chloroquine in COVID-19 from an international collaborative meta-analysis of randomized trials. Nat Commun. 2021; 12(1):2349. Doi: 10.1038/s41467-021-22446-z