ORIGINAL ARTICLE

Hydroxychloroquine for COVID-19: A Single Center, Retrospective Cohort Study

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ABSTRACT

Introduction: The outbreak of coronavirus disease (COVID-19) in December 2019 called for a rapid solution, leading to repurposing of existing drugs. Due to its immunomodulatory effect and antiviral properties, hydroxychloroquine (HCQ) has been used in early 2020 for treatment of COVID-19 patients. This study was conducted to evaluate the treatment outcome of HCQ monotherapy in Malaysia. Methods: A retrospective cohort study was conducted in COVID-19 ward in Hospital Kuala Lumpur (HKL), from March to April 2020. A total of 446 COVID-19 patients were recruited, only 325 patients were finally included for analysis. Statistical analysis was done using SPSS, with a significant value set at p<0.05. Results: The mean age of the patients were 38.5 ±15.5. They were majority male, (n=210, 64.6%) Malaysian (n=239, 73.5%) and Malay ethnicity (n=204, 62.8%). Ninety-one (28%) patients received HCQ monotherapy. HCQ monotherapy was associated with worse outcome (OR: 10.29, 95% CI 1.17-90.80). There was a significant difference in mean length of stay between those with and without HCQ treatment (t323=5.868, p<0.001, 95% CI, 2.56-5.31). The average length of stay for HCQ treated group was 3.84 days longer than those without treatment. 6.6% of the patient receiving HCQ monotherapy encountered adverse drug effects. Conclusion: Similar to study reported worldwide, our study demonstrated that HCQ did not improve length of stay and the outcome of COVID-19 patients.  

Key words: Hydroxychloroquine, COVID-19, Coronavirus, Antiviral, Efficacy

INTRODUCTION

The world is still devastated by Coronavirus Disease 2019 (COVID-19) since it first reported in December 2019. Until February 2022, World health organization (WHO) has reported up to total of 400 million confirm cases with 5 million deaths worldwide (1). Novel oral antivirals such as Molnupiravir and Paxlovid are found to be effective in reducing the mortality and hospitalization rates in patients with COVID-19, but are not readily available in most of the countries (2). In the beginning of this pandemic, few drugs with antiviral property such as Molnupiravir and Paxlovid are found to be effective in reducing the mortality and hospitalization rates in patients with COVID-19, but are not readily available in most of the countries (2). In the beginning of this pandemic, few drugs with antiviral property such as Chloroquine (CQ), Hydroxychloroquine (HCQ), Remdesivir and Lopinavir / Ritonavir, were being repurposed and used as off-label medications to fight COVID-19 (3). CQ and its safer hydroxyl analogue HCQ have been widely used as an antimalarial (4). Moreover, HCQ is used as an immunomodulator and anti-thrombotic in various autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis and antiphospholipid syndrome (5). The studies of CQ’s antiviral properties are dated back to the late 1960s (6). CQ and HCQ antiviral properties were supported by in vitro study. Liu et al and Wang et al demonstrated that CQ and HCQ are able to inhibit entry, duplication and release of SARS-CoV-2 in infected kidney epithelial cells of African green monkey by glycosylation of ACE2 receptors and increase endosomal pH (7-9). Based on pharmacokinetic models for treatment of COVID 19, Yao et al suggested the optimal dosage of HCQ will be 400mg twice daily on day one and 200mg twice daily for another 4 days (8). Positive results from in vitro study have led to off-label uses as well as clinical trials of CQ and HCQ worldwide to combat COVID-19. The positive results from France and China have motivated large scale multicentred and international clinical trial (10-12). Nonetheless, more recent evidence has found...
no benefit in using HCQ in COVID-19 and thus FDA has revoked the use of HCQ and CQ (13-16). When the disease first struck Malaysia in early 2020, HCQ was used as an off-label treatment against COVID-19 in many centres in Malaysia, including Hospital Kuala Lumpur. In order to determine the outcome of HCQ treated COVID-19 patients among our own population, we had conducted this retrospective comparative cohort study.

MATERIALS AND METHODS

Study design
This was a single-centre retrospective cohort study done in Hospital Kuala Lumpur. This study had obtained approval from Medical Research & Ethics Committee, Ministry of Health in May 15, 2020. (KKM/NIHSEC/ P20-1099 (6)).

Study population
All patients aged above 18 years admitted to COVID-19 wards in Hospital Kuala Lumpur (HKL) with or without HCQ monotherapy from 1st March 2020 to 30th April 2020 were included in this study. Children and those who were on treatment other than HCQ monotherapy were excluded from analysis.

Data collection
Patients’ hard copy health medical records were retrieved from the hospital record office and data collection was conducted using a structured data collection form. Data collected include demographic parameters, clinical symptoms and severity of COVID-19 according to category (Category 1, asymptomatic patient; Category 2, symptomatic patient but absent of pneumonia; Category 3, symptomatic patient with pneumonia; Category 4, symptomatic patient with pneumonia and requiring oxygen supplementation; Category 5, critically ill with multiorgan involvement.) (17). HCQ was indicated patient with category 2 plus warning signs of further deterioration, category 3, category 4 and category 5 disease. (Supplementary data for full information) Day of illness where HCQ was initiated and total duration of treatment were collected as well.

Patients who received HCQ monotherapy (Dose: 800mg/day on day one, follow by 400mg/day for 4 days) were compared to patients who did not receive HCQ monotherapy.

The primary outcome of this study was difference in clinic response (improved or worsened) between the two cohorts, with or without HCQ monotherapy. Improved clinical response was defined as discharged well from hospital and worsened clinical response was defined as increased requirement in oxygen supplementation, requiring non-invasive ventilation, invasive ventilation, or ICU admission and death. Secondary outcomes include length of hospital stay and side effects of HCQ.

Statistical analysis
Qualitative variables were expressed in frequency and percentage while quantitative variables were expressed in mean with standard deviation. Statistical evaluation was utilized to determine if there is association in the distribution of variables (Chi-Square test) between HCQ and non HCQ cohorts, Chi-Square test was used for categorical variables and Student T test was used for continuous variables. All analyses were conducted using IBM SPSS Statistics version 26 where p value of <0.05 was considered statistically significant.

RESULTS

A total of 446 COVID-19 patients were admitted to HKL from March 1 2020 to April 30 2020. 84 patients were excluded as they were on treatment other than HCQ monotherapy. One patient was excluded due to incomplete information. 27 patients were excluded due to age less than 18-year-old and 9 patients were excluded due to duplicate record. Finally, 325 patients were included for analysis. These patients were separated into two groups namely HCQ (n=91) and non-HCQ (n=234). (Figure 1).

Demographic
64% of the patients were male with mean age of 39.5 ± 15.6 years. Most of the patients were Malaysian (73.5%, n=239). In terms of ethnicity, Malays were the majority (62.8%, n=204), followed by Chinese (9.5%, n=31), Indian (4.3%, n=14) and others (23.4%, n=76). More than half of the patients presented with Category 2 (51.7%, n=168) followed by Category 1 (42.2%, n=137), Category 3 (4%, n=13), Category 4 (1.5%, n=5) and
Category 5 (0.6%, n=2). Majority of the patients were symptomatic (65.2%, n=212). Cough, fever, sore throat, and runny nose were the most common manifesting symptoms (40.6%, n=130; 40%, n=132; 17.8%, n=58; 12.3%, n=40; respectively). Gastrointestinal symptoms such as diarrhoea, vomiting and nausea were recorded in 71.1% (n=23), 1.5% (n=5) and 0.9% (n=3) of the patients.

**Student t Test**

Among the HCQ cohort, HCQ was initiated within a mean 8.05 ± 6.42 days of illness. The mean duration of treatment was 6.4 ± 2.75 days. There was no statistical difference in terms of gender, age, nationality, and comorbidities between both cohorts. However, severity of the illness on presentation and presence of symptoms were found to have significant association with p value of <0.001 and 0.006 respectively (Table I).

**Primary Outcome**

95.6% (n=87) of those who received HCQ had recovered while 99.6% (n=233) of those not receiving HCQ had recovered. This difference was significant (p = 0.009, OR: 10.29; 95% CI 1.17-90.80). More patients in the HCQ arm were reported to have deteriorated (n= 4), while only one from the non-HCQ cohort experienced the same. Among patients who deteriorated, two required invasive ventilation, one required treatment escalation, one transferred to intensive care unit, and one transferred to another facility for advance care but we were unable to trace further information (Table II).

### Table I: Demographic characteristics

<table>
<thead>
<tr>
<th>Category</th>
<th>Initiated (n=91)</th>
<th>Not initiated (n=234)</th>
<th>Total</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male</td>
<td>Female</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>54 (59.3)</td>
<td>47 (66.7)</td>
<td>210 (64.6)</td>
<td>0.215</td>
</tr>
<tr>
<td>Age, Mean (SD)</td>
<td>42.19</td>
<td>38.46</td>
<td>38.5</td>
<td>0.111**</td>
</tr>
<tr>
<td>Nationality</td>
<td>Malaysian</td>
<td>Non-Malaysian</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>63.0 (69.2)</td>
<td>28 (30.8)</td>
<td>217 (70.6)</td>
<td>0.272</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Malay</td>
<td>Chinese</td>
<td>47 (67.2)</td>
<td>0.042</td>
</tr>
<tr>
<td></td>
<td>49 (53.8)</td>
<td>15 (16.5)</td>
<td>64 (64.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Indian</td>
<td>Others *</td>
<td>4 (4.4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>13 (10.9)</td>
<td>12 (23.5)</td>
<td>15 (10.9)</td>
<td></td>
</tr>
<tr>
<td>Severity on Presentation</td>
<td>Category 1</td>
<td>Category 2</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>21 (23.1)</td>
<td>53 (58.2)</td>
<td>174 (17.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Category 3</td>
<td>Category 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 (11)</td>
<td>5 (5.5)</td>
<td>15 (11)</td>
<td></td>
</tr>
<tr>
<td>Comorbidities</td>
<td>Diabetes Mellitus</td>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>34 (38)</td>
<td>39 (67.2)</td>
<td>73 (17.8)</td>
<td>0.737</td>
</tr>
<tr>
<td></td>
<td>Dyslipidaemia</td>
<td>Ischaemic Heart Disease</td>
<td></td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>2 (2.2)</td>
<td>11 (4.6)</td>
<td>13 (4.6)</td>
<td>0.301</td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
<td>Asthma</td>
<td></td>
<td>0.532</td>
</tr>
<tr>
<td></td>
<td>0 (0)</td>
<td>3 (4.5)</td>
<td>3 (4.5)</td>
<td></td>
</tr>
<tr>
<td>Presence of symptoms</td>
<td>Yes</td>
<td>No</td>
<td></td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>70 (76.9)</td>
<td>21 (23.1)</td>
<td>91 (76.9)</td>
<td></td>
</tr>
</tbody>
</table>

**Secondary Outcome**

A numerical longer mean length of stay was observed in the HCQ cohort, (12.45 ± 6.872 days vs 8.61 ± 4.553 days, (t323=5.868, p<0.001, 95% CI 2.56-5.31) (Figure 2). Among those who received HCQ, 6.6% (n=6) experienced adverse effects. Transaminitis (3.3%, n=3) was the most common adverse effect followed by combined acute liver and kidney injury (2.2%, n=2). Only one (1.1%) patient reported to have gastrointestinal side effect.

![Figure 2: Total Length of Stay](image)

**DISCUSSION**

In this study, we observed that those who were treated with HCQ had worse clinical outcome compared with the control group. This result contradicts with few studies done in France and China in the early pandemic that supported the use of HCQ/CQ in COVID-19. Gautret et al from France conducted an open label non-randomized clinical trial where he reported that viral clearance at day 6 was significantly higher in the HCQ treatment group. However, the study was underpowered due to its small sample size (n= 42) and high dropout rate (n=6, 16.7%). In addition, viral clearance may not always translate to clinical improvement, therefore, trial that examine clinical outcome was warranted. (10) Gautret et al recruited another 80 patients treated with HCQ in combination with Azithromycin where they reported that 81.3% of patients had favourable clinical
outcome. Nevertheless, this study does not have a control arm to compare with (11). On the other hand, Chen et al. from China reported significant reduction in mean day of fever 3.2 ±1.3 days vs 2.2 ±0.4 days, \( p=0.0008 \) and cough 3.1 ±1.5 days vs 2.0 ±0.2 days, \( p=0.0016 \) between the control group and patients who received HCQ respectively. In addition, Chen et al. observed significant difference in resolution of pneumonia from computed tomography of the chest between patients treated with HCQ and control group, 80.6% vs 54.8%, \( p=0.0476 \) respectively. The sample size of this study was small (\( n=62 \)) and there was no report on patients’ clinical outcome although 4 patients from the control group were reported to have progressed into severe disease (12).

Larger scale, well-designed, multi-center, randomized controlled trials exhibited contradictory findings. WHO Solidarity Trial, an open label randomized controlled trial of 4 repurposed antiviral drugs namely Remdesivir, HCQ, Lopinavir, and Interferon beta-1a on hospitalized patient with COVID-19 in 30 countries including Malaysia, 947 patients were randomized into HCQ group and 906 patients were in the control group. There was no significant difference in 28 days mortality rate between the HCQ (n=104) and control group (n=84), (rate ratio, 1.19; 95% CI, 0.86-1.59) (13). In the United Kingdom, RECOVERY trial was another open label randomized controlled trial conducted to examine 28 days mortality in patients received HCQ. They found patients treated with HCQ had no statistically significant reduction in 28 days mortality. Death occurred in 27% of the patients in HCQ group versus 25% in the control group. (Risk Ratio, 1.09; 95% CI, 0.97-1.23; \( p=0.15 \)) (14). A meta-analysis involving 10012 patients showed that patients treated with HCQ had higher all-cause mortality with odd ratio of 1.11, 95% CI: 1.02-1.20. (15) This analysis showed 24% risk reduction in composite outcome of COVID-19 infection, hospitalization and death. Analysis showed 24% risk reduction in composite outcome of COVID-19 infection, hospitalization and death. However, in the study, mean day of illness for initiation of treatment was 8.05 days (±6.425), Therefore, our study was not able to examine efficacy of HCQ in early course of the disease which may result in favourable outcome.

We found that HCQ appeared to be a safe drug with minimal side effect. Gastrointestinal side effects such as nausea, abdominal discomfort, vomiting and diarrhoea were the most common side effects reported in previous studies (23). However, only one patient was found to have gastrointestinal side effect in our study. Worth to mention, the gastrointestinal symptoms can be presenting symptom of COVID-19, leading to confusion (24). Cardiac arrhythmia is one of the main concern in the use of HCQ especially when concomitant arrhythmogenic drugs were administered such as Azithromycin and Remdesivir. (25). We found no such worry in our study. HCQ is metabolized in the liver and have some metabolites cleared by the kidney (26). However, COVID-19 may also contribute to kidney or liver impairment (27). Liver and kidney impairment were observed in three of the patients, but may not solely caused by the drug itself. Nevertheless, HCQ should be used in caution with patients with underlying liver and kidney disease.

One of the limitation of this study is this is a retrospective observational study therefore there is lack of blinding...
and randomization. Patients with more severe illness started with other medications such as dexamethasone, methylprednisolone, and lopinavir/ritonavir were excluded from this study. As a result, this cohort consists of patients with milder disease. Patients started with other medication together with HCQ were excluded in this study as well. Thus, we are unable to determine effect of combination therapy. There is also an observed discrepancy between the severity of the disease in both groups, which may have led to a bias result.

CONCLUSION

Consistent with larger trials conducted worldwide, this retrospective cohort study found that HCQ failed to show any benefit in improving clinical outcome or reducing length of hospital stay in patients with COVID-19. Thus, this study further augments the fact that HCQ use in COVID-19 is not encouraged.

ACKNOWLEDGEMENT

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REFERENCES

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