Short Communication

Hydroxychloroquine use in hospitalised patients with COVID-19: An observational matched cohort study

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ABSTRACT

Aim: To assess the efficacy and safety of hydroxychloroquine with or without azithromycin) in hospitalized adult patients with COVID-19.
Methods: We utilized a hospital based prospective data registry. The primary end point was to assess the impact of hydroxychloroquine with or without azithromycin, on outcome, length of hospitalization, and time to clinical improvement. We utilized treatment effects with inverse-probability-weighting and Cox proportional hazards models. All analyses accounted for age, gender, race, severity on admission, days from symptoms onset and chronic comorbidities.
Results: 36 patients received hydroxychloroquine and were age- and sex-matched to 72 patients with COVID-19 who received supportive care. Compared to supportive care, the use of HCQ did not shorten the time to clinical improvement (+0.23 days; 95% CI: −1.8–2.3 days) nor did it shorten the duration of hospital stay (+0.91 days; 95% CI: −1.1–2.9 days). Additionally, HCQ did not decrease the risk of COVID-19 in-hospital death (aHR 1.67; 95% CI: 0.29–9.36). Finally, we observed a slight QTc prolongation from a baseline of 444 ± 26 ms to 464 ± 32 ms (mean±SD) among patients receiving hydroxychloroquine with or without azithromycin.
Conclusion: This study did not yield benefits from hydroxychloroquine use in patients with COVID-19 and monitoring for adverse events is warranted. Nevertheless, the treatment was safely studied under the guidance of an antimicrobial stewardship program.

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Hydroxychloroquine (HCQ) and chloroquine were among the first drugs that emerged as potential therapeutic options against coronavirus disease 2019 (COVID-19). These two antimalarial drugs, also commonly used as immunomodulators in the setting of rheumatological diseases, showed in vitro activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1,2]. The aim of this study was to assess the efficacy and safety of HCQ, with or without azithromycin (AZM), in hospitalised adult patients with COVID-19.

Data from the largest healthcare network in Rhode Island, USA, were utilised with the aim of exploring the efficacy and safety of HCQ in hospitalised patients with COVID-19. The primary endpoint was to assess the impact of HCQ, with or without AZM, on mortality, length of hospitalisation and time to clinical improvement. Treatment effects with inverse probability weighting and Cox proportional hazards models were utilised. All analyses accounted for age, sex, race, disease severity on admission, days from symptom onset and chronic co-morbidities.

There were no significant differences between the two groups (HCQ ± AZM versus supportive care) in terms of illness severity at the time of hospital admission (Table 1). In the inverse probability analyses, the average treatment effects (ATEs) of HCQ on multiple clinical outcomes were estimated. First, the impact of HCQ on the time to clinical improvement was assessed, measured as an improvement of two points in a six-category ordinal scale (not

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Table 1
Baseline patient characteristics on hospital admission[a].

Characteristic	Total (n = 108)	SC (n = 72)	HCQ (n = 36)	P-value
Age (years) [median (IQR)]	58.5 (45–69.5)	56.5 (43–71.5)	61 (48.5–67.5)	0.68
Patient sex				1.00
Male	57 (52.8)	38 (52.8)	19 (52.8)	
Race				0.28
Black or African-American	17 (15.7)	9 (12.5)	8 (22.2)	
Hispanic	43 (39.8)	27 (37.5)	16 (44.4)	
Other	2 (1.9)	2 (2.8)	0 (0.0)	
White	46 (42.6)	34 (47.2)	12 (33.3)	
Chronic co-morbidities				
Congestive heart failure	13 (12.0)	8 (11.1)	5 (13.9)	0.68
Cardiac arrhythmia	17 (15.7)	12 (16.7)	5 (13.9)	0.71
Valvular disease	4 (3.7)	4 (5.6)	0 (0.0)	0.15
Pulmonary circulation disorders	6 (5.6)	6 (8.3)	0 (0.0)	0.075
Peripheral vascular disorders	3 (2.8)	1 (1.4)	2 (5.6)	0.21
Hypertension	42 (38.9)	25 (34.7)	17 (47.2)	0.21
Diabetes	36 (33.3)	21 (29.2)	15 (41.7)	0.19
Neurological disorders	10 (9.3)	6 (8.3)	4 (11.1)	0.64
Chronic pulmonary disease	20 (18.5)	7 (9.7)	13 (36.1)	<0.001
Hypothyroidism	10 (9.3)	6 (8.3)	4 (11.1)	0.64
Renal failure	14 (13.0)	6 (8.3)	8 (22.2)	0.043
Liver disease	5 (4.6)	3 (4.2)	2 (5.6)	0.75
Solid tumour without metastasis	4 (3.7)	3 (4.2)	1 (2.8)	0.72
Obesity	45 (41.7)	27 (37.5)	18 (50.0)	0.21
National Early Warning Score (mean ± S.D.)	3.92 (2.53)	3.93 (2.73)	3.89 (2.11)	0.94
Elixhauser–van Walraven score (mean ± S.D.)	3.47 (7.52)	2.94 (7.23)	4.53 (8.06)	0.30
Days from symptoms onset (IQR)	5 (2–7.5)	4 (1–7)	6 (2–9)	0.083

SC, supportive care, HCQ, hydroxychloroquine; IQR, interquartile range; S.D. standard deviation.
[a] Data are n (%) unless otherwise stated.

hospitalised; hospitalised, not requiring supplemental oxygen; hospitalised, requiring low-flow supplemental oxygen; hospitalised, on non-invasive ventilation or high-flow oxygen; hospitalised, on invasive mechanical ventilation; and death due to COVID-19). Compared with supportive care, for which the mean time to clinical improvement was 6.96 days, the ATE of HCQ was not significant [+0.23 days, 95% confidence interval (CI) −1.87 to 2.33 days]. Similarly, compared with supportive care, HCQ did not shorten the hospital length of stay in patients with COVID-19 (ATE, +0.91 days, 95% CI −1.15 to 2.98 days). Moreover, patients who received HCQ did not experience less time to fever resolution compared with supportive care (HCQ ATE, +1.27 days, 95% CI −0.49 to 3.03 days).

Cox proportional hazards models were utilised to estimate in-hospital risk of death due to COVID-19. In the unadjusted model, compared with the supportive care arm, HCQ did not decrease the risk of in-hospital death [hazard ratio (HR) = 1.10, 95% CI 0.31–3.93). Moreover, HCQ did not appear to decrease the risk of death even after adjusting for age, sex and race [adjusted HR (aHR) = 0.82, 95% CI 0.20–3.24] as well as days from symptoms onset, National Early Warning Score (NEWS) and Elixhauser–van Walraven score (aHR = 1.67, 95% CI 0.29–9.36). Finally, using the Schoenfeld residuals method, proportionality was tested and no violations of the proportional hazard assumption were identified in any of the models.

Among 36 patients who received HCQ, 32 patients received HCQ with AZM, whilst 4 patients received HCQ monotherapy due to prolonged QTc interval at baseline. Five patients did not complete their 5-day regimen. The reasons behind discontinuing HCQ were as follows: one patient developed QTc prolongation (484 ms) (Day 3); one patient died due to COVID-19 (Day 3); one patient developed bradycardia (Day 4); in one patient the treating team discontinued the drug owing to possible contribution to the patient's altered mental status (Day 3); and in one patient the treating team decided to discontinue the drug due to seizure activity during hospitalisation (Day 4). In addition, although not included in the current analysis owing to the receipt of less than four doses, one patient discontinued HCQ after three doses owing to QT prolongation (453 ms) and the development of premature ventricular contractions. After performing a paired t-test, QTc prolongation from a baseline of 444 ± 26 ms (mean ± standard deviation) to 464 ± 32 ms was observed (P < 0.001). A comparison between HCQ monotherapy and HCQ + AZM was not performed due to the small number of patients receiving HCQ monotherapy. Finally, among patients who completed their 5-day regimen, three patients developed QTc > 500 ms. None of the included patients developed torsades de pointes.

Overall, this study did not yield definite benefits from HCQ use in patients with COVID-19; however, the results should be interpreted with caution due to the limited sample size. A recent report from the USA with 1376 patients, of whom 811 (58.9%) received HCQ, found no significant association between HCQ use and intubation or death (HR = 1.04, 95% CI 0.82–1.32) [3], whilst another report of 368 US veterans also found no evidence that HCQ use reduced the risk of mechanical ventilation and mortality [4]. Similarly, a report from France studying 181 patients with COVID-19 pneumonia found no difference in terms of mortality and intensive care unit (ICU) admission in patients treated with HCQ compared with the standard of care [5]. Importantly, as COVID-19 treatments require testing and monitoring, these results underscore the need for close monitoring of these patients under the guidance of an antimicrobial stewardship programme (ASP). As is the case with non-COVID patients, ASP oversight is key to optimise effectiveness and to minimise side effects.

Conflict of interest

None.

Ethical approval

This study received ethical approval from the Institutional Review Board (IRB) of the Rhode Island Hospital (Providence, RI, USA) [ref. #005120].

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jgar.2020.07.018.

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