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Internal Medicine Section

Implementing a Fever Clinic for Managing COVID-19 Patients using Hydroxychloroquine Protocol- An Experience from a Primary Healthcare Centre in Riyadh, Saudi Arabia

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ABSTRACT

Introduction: During the initial weeks of the COVID-19 pandemic, there was limited information and evidence about therapeutic interventions for management of COVID-19 infections. Consequently, fever clinics were established in Saudi Arabia to provide supportive treatment for all COVID-19 patients as specialised clinics. During the early months of 2020, Hydroxychloroquine (HCQ) was being used as part of the Saudi Ministry of Health (MoH) protocol for management of COVID-19 infections.

Aim: To report the experience with implementing fever clinic utilising the HCQ-based protocol for adults with mild and moderate symptoms of COVID-19, and provide further evidence regarding the efficacy and safety of HCQ.

Materials and Methods: A prospective observational study was conducted in one of the primary healthcare centres in Saudi Arabia. All patients with suspected or confirmed COVID-19 who visited the fever clinic and met the eligibility criteria of starting HCQ based protocol were included in the study. Beside supportive treatment, the intervention dose of HCQ was 400 mg twice a day for one day followed by 200 mg twice a day for another four days. Statistical Package for Social Sciences (SPSS) version 22 was used for data analyses.

Results: A total of 108 patients with mean age of 36 years with Standard Deviation (SD) of 9.3 were included in the study. The mean Body Mass Index (BMI) was 27.1 (SD 4.9). In addition, 73.1% of the patients were males and 25% were smokers. The study findings showed that the fever clinic was effective in managing the symptoms of COVID-19 and treating the patients regardless of the use or completion of HCQ. In particular, on day 6, cough improved in >85% of the patients and fever was resolved in >83% of patients. However, there were no statistically significant differences among the patients who received/completed HCQ and those who did not start or complete the protocol in terms of negative conversion based on the Nasopharyngeal (NP) swab real time Reverse-Transcriptase Polymerase Chain Reaction (RT-PCR) by day 14, and resolution/improvement of symptoms on day 6 ($p>0.05$).

Conclusion: This study documented the experience of implementing a fever clinic to manage the suspected and confirmed COVID-19 patients with mild to moderate symptoms during the initial phase of the pandemic in Saudi Arabia. The study findings revealed that the concept of fever clinics was useful for managing suspected and confirmed cases. At the same time, there were no additional benefits of HCQ compared to the supportive treatment in this study.

Keywords: Coronavirus disease-2019, Cough, Pandemic, Symptoms

INTRODUCTION

The COVID-19 infections are increasing rapidly throughout the world and this novel virus has crossed the frontiers [1,2]. The infected individuals from COVID-19 can develop flu or pneumonia-like symptoms and in severe cases, it can lead to multi-organ failure [3]. This highly contagious disease spreads from one individual by body secretions such as saliva or nasal droplets and it can also pass from human to the next by coming in contact with the infected individual or by touching the infected areas [4,5]. The virus started its journey in one of the provinces of China, named Wuhan, at the end of 2019 and spread with great speed through China and the rest of the world [6]. Overall, a peak in the number of cases was usually followed by a decline when timely control measures were taken [7]. Despite the effective and timely measures, almost all of the developed and developing countries have faced substantial morbidity and mortality from this unanticipated pandemic [8,9].

Since COVID-19 poses a severe threat to global health, therefore, there is an urgent need to cure symptomatic patients and to limit the transmission in the community and to reduce the morbidity and mortality associated with COVID-19 [10,11]. Consequently, many countries including Saudi Arabia established fever clinics to manage suspected cases of COVID-19 infections. These clinics serve all individuals who show COVID-19 symptoms such as fever, sore throat, muscle pain, shortness of breath, loss of taste or smell. The fever clinics receive patients at any time, without appointments for appropriate management of COVID-19 infections [12]. In addition to this benefit, the clinics help to reduce the potential of further infections as the patients will be treated in separate clinics under strict infection control and precautionary measures rather than mixing with other patients in emergency department and ordinary medical clinics.

However, numerous drugs have been given to the patients of COVID-19 due to their well-known antiviral pharmacological actions hoping for potential effectiveness against COVID-19 infections [13,14]. The absence of a proven therapy for Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection has encouraged clinicians to use drugs that have been found effective for other medical conditions [15]. For example, HCQ is being widely prescribed by physicians for COVID-19 patients on the basis of the results from some observational evidence (including a preprint) at the early months of the pandemic [16-18]. Chloroquine or HCQ have been used as they have shown beneficial results

in-vitro and have also been used in the past for diseases similar to COVID-19 [13,14,19].

It has been postulated that that drugs such as HCQ suppresses the SARS-CoV-2 replication by hindering the production of pro-inflammatory cytokines thus blocking the inflammatory cascade that causes acute respiratory distress syndrome [20]. However, some of the observational studies initially suggested positive results of HCQ, while others have shown lack of effectiveness of this drug [21,22]. Therefore, the investigators aimed to report experience from the fever clinic established during the early phases of the pandemic with assessment of the patients' outcomes receiving the HCQ, besides supportive treatment in adults with mild and moderate symptoms of Coronavirus Disease-2019. This could help in providing further guidance especially during uncertain times of pandemics.

MATERIALS AND METHODS

A prospective observational study was conducted at the fever clinic of Wazarat Healthcare Centre (WHC) in Family and Community Medicine Department, which is a primary healthcare centre of Prince Sultan Military Medical City (PSMMC) in Riyadh, Saudi Arabia and it was accredited by Joint Commission International (JCI). The fever clinic was established during COVID-19 pandemic in Saudi Arabia and was established mainly to manage and follow-up stable suspected and confirmed COVID-19 mild and moderate cases attending the primary healthcare centre. The research ethics committee-Prince Sultan Military Medical City (PSMMC) approved the protocol of the study (HP-01-R097).

All patients attending the fever clinic with suspected or confirmed COVID-19, between 14th June 2020 to 3rd August 2020 who met the eligibility criteria of starting HCQ were included in the study. Patients were informed about the study and its objectives with all relevant information. Consequently, the patients who provided an informed consent were included in the study. In addition, they were informed about their right to withdraw from the study at any time.

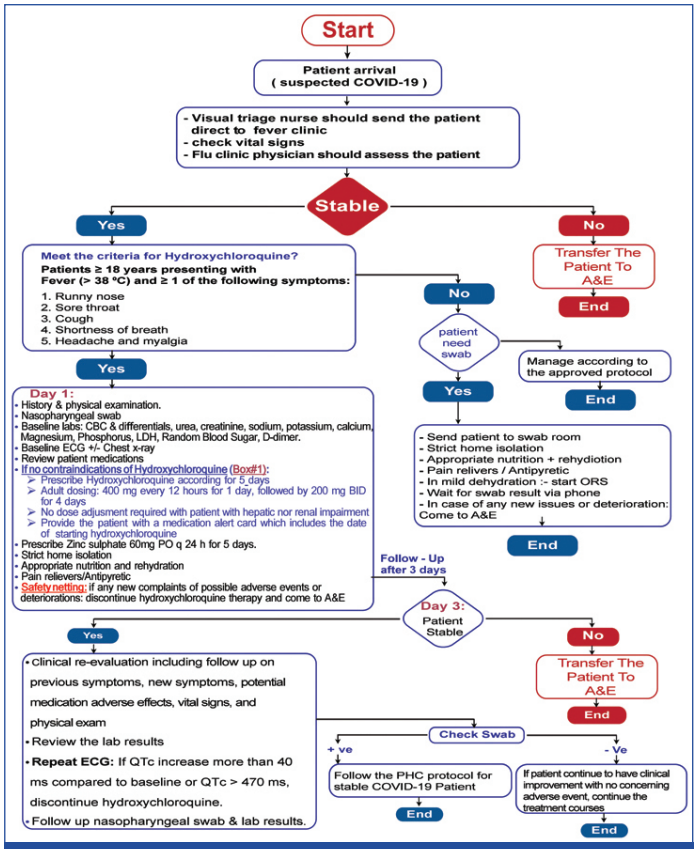
Inclusion criteria: The eligibility of the patients for HCQ based protocol included patients' between 18 years to 65 years of age.

Exclusion criteria: Severely ill patients with heart block, and arrhythmias; severe liver disease; pregnancy or lactation; retinopathy, and other retinal diseases; allergy to sulfa drug and patients with G6PD deficiency were excluded from the study.

Clinical Protocol of the Fever Clinic and HCQ for Treatment

The fever clinic protocol for management of suspected and confirmed COVID-19 cases are summarised in [Table/Fig-1]. The protocol of HCQ was formed to manage and follow-up for stable and confirmed mild to moderate COVID-19 cases who attended primary healthcare centre for this purpose. This was adapted from approved Saudi MoH protocol at that time during the initial phase of the pandemic [23]. As per the Saudi MoH protocol, HCQ was considered for all patients visiting the fever clinic aged ≥18 years, presenting with documented temperature of >38°C within the last 24 hours and suffered atleast from runny nose, sore throat, cough, shortness of breath, headache, and/or myalgia. In addition to the history taking and physical examination, NP swab and other laboratory investigations such as electrolyte, haemoglobin level, white blood cells, D-Dimer, serum creatinine were done before starting the treatment. The patients were re-evaluated when the first swab PCR result was out.

Informed consent was taken from patients that were administered the medication. As per the protocol, HCQ was initiated and accounted as day 1 with 400 mg every 12 hours (for 1 day) followed with 200 mg every 12 hours for 4 days with zinc 60 mg OD. All patients with confirmed COVID-19 were enrolled in the study and who met the inclusion criteria for starting HCQ. Diagnosis and classification



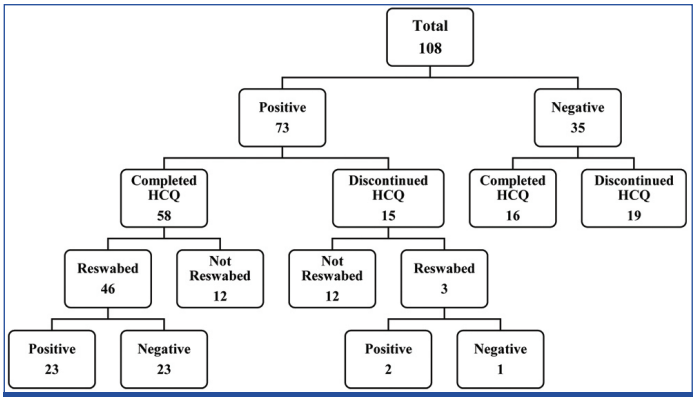
[Table/Fig-1]: Fever clinic protocol for management of suspected and confirmed COVID-19 cases.

of COVID-19 was based on the criteria of the Saudi Arabia Ministry of Health Protocol, June 2020 [23]. ECG was done at baseline and on day 3. If the QT Interval (QTc) was exceeding 470 ms during initial measurement on day 1, HCQ was not initiated. In day 3, if QTc exceeded 470 ms or increased more than 40 ms from baseline, HCQ was discontinued. Patients who showed clinical deterioration at day three, were referred to the hospital and continuous follow-up was done by the research team for outcomes.

The collected data included demographic and general patient information, vital signs, and Electrocardiogram (ECG) and if the QTc >470 ms, the HCQ was not be started. Chest X-ray was done when it was clinically indicated. Co-morbidities were assessed to improve safety during the use of HCQ. Safety outcome of the treatment protocol, including the percentages of patients who developed side-effects (ECG changes, GI symptoms, nausea and headache), and reasons for medication discontinuation was recorded. Results of laboratory tests done on day 1 were reviewed and repeated on day 3. ECG was repeated and QTc was measured, if it exceeded >470 ms or increased more than 40 ms compared to baseline, the medication was stopped immediately.

Patients' Follow-up and Outcomes Monitoring

Clinical symptoms were re-evaluated after treatment administered and temperature was also recorded. On day 6 follow-up, alleviation of clinical symptoms were assessed in comparison to day 1. On the other hand, a second NP swab real time RT-PCR, was taken to assess negative conversion of coronavirus on day 14. According to the WHO guidelines, during the early phase of the pandemic, a positive result of (RT-PCR) based on a NP swab was considered as a confirmed case of COVID-19. Adherence to the prescribed dose of HCQ was assessed during the follow-up period. Flow chart of the study is shown in [Table/Fig-2] and demonstrates the response of participants on day 1, 3, 6 and 14. The outcomes for the fever clinic-based protocol included COVID-19 negativity test, which was measured at day 14 after using HCQ. Negative conversion of COVID-19 was based on atleast one laboratory report. The second outcome was resolution of symptoms.



[Table/Fig-2]: Flow chart of the participants of study by day 1, 3, 6 and 14.

STATISTICAL ANALYSIS

Continuous data were presented as means±SD and categorical data were presented as frequencies (n) and percentages (%). The level of p-value <0.05 was used for all analyses to indicate a statistical significance. Chi-square test and Fisher-exact test was used to compare the differences across categorical variables for HCQ usage. Statistical Package for the Social Science (SPSS) version 22 was used for data analyses.

RESULTS

Socio-demographic and clinical characteristics of the patients: The mean age of the 108 patients was 36 years (SD 9.3) and mean BMI was 27.1 kg/m^2 (SD 4.9). In addition, 73.1% of the patients were males and 25% were smokers [Table/Fig-3]. Moreover, regarding clinical parameters of the patients, 4.6% of the patients were diabetic, 5.6% were hypertensive and none were suffering from other co-morbidities (congestive heart failure, recent myocardial infarction, active malignancy, immunosuppressive illness, G6PD deficiency, retinopathy). The mean systolic and diastolic pressure at the time of admission was 118.9 (SD 14) and 75.7 (SD 9.6), respectively. The mean heart rate was 101.12 (SD 18.2) and mean haemoglobin (gm/dL) was 14.2 (SD 1.69). The mean value for temperature was (37.59±0.89), and the mean value for D-Dimer was (1.38±2.20). All patients were febrile, and 79.6% had cough at the initial presentation. None of the patients had abnormal ECG including QTc interval prolongation.

Continuous variables	Mean	Standard deviation
Age (Years)	36	9.3
BMI (kg/m^2)	27.1	4.9
Systolic blood pressure (mmHg)	118.9	14.0
Diastolic blood pressure (mmHg)	75.7	9.6
Heart rate (BPM)	101.12	18.2
Haemoglobin (gm/dL) 11.5-16.5 g/dL)	14.2	1.69
Temperature (Degree celsius)	37.59	0.890
Serum creatinine (45-84 umol/L)	81.18	17.97
GFR (mL/min/1.73 m^2)	99.28	24.54
TSH (0.27-4.200 U in/mL)	2.06	1.36
Sodium (136-145 mmol/L)	137.8	3.63
Potassium (3.5-5.1 mmol/L)	4.74	0.54
Magnesium (0.85-1.10 mmol/L)	0.86	0.09
Phosphate (0.81-1.45 mmol/L)	0.96	0.23
Calcium (2.15-2.50 mmol/L)	2.22	0.12
Platelet count (150-450×10^9/dL)	250.44	68.33
D-Dimer (0.000-500 ug/mL)	1.38	2.20
WBC (4.0-11.0×10^9/dL)	6.00	2.65
ANC (Median and IQR)	2.65	2.80
Categorical variables	**n**	**%**
Gender		
Male	79	73.1
Female	29	26.9
Smoking status		
No	81	75
Yes	27	25
History of alcohol		
No	107	99.1
Yes	1	0.9
Allergy to sulfonamides		
No	75	69.4
Unknown	33	30.6
Co-morbidity		
Diabetes mellitus	5	4.6
Hypertension	6	5.6
Cough		
No	22	20.4
Yes	86	79.6
Fever		
No	0	0
Yes	108	100
Result of the nasopharyngeal swab		
Negative	35	32.4
Positive	73	67.6
ECG		
Normal	108	100
Abnormal	0	0
Chest X-ray		
Normal	5	4.6
Abnormal	1	0.9
Not done	102	94.4
Liver function tests		
Normal	96	88.9
Abnormal	1	0.9
Not done	11	10.2
Oxygen saturation		
≥94%	100	92.6
<94%	8	7.4
History of any medications		
Macrolides (Azithromycin)	4	3.7
Antihistamine	1	0.9
Antihypertensive	3	2.8
Antidepressant	1	0.9
Fluoroquinolones	1	0.9
Antimalarial	0	0
Antiemetic	0	0
Antifungal	0	0
Antipsychotic	0	0
Anticancer medication	0	0
Immunosuppressive medication	0	0

[Table/Fig-3]: Baseline Socio-demographic and clinical characteristics of the patients enrolled in the Primary Care Centres before starting HCQ (n=108).
GFR: Glomerular filtration rate, TSH: Thyroid stimulating hormone, WBC: White blood cells, ANC: Absolute neutrophil count

Clinical outcomes of the patients treated at the fever clinic using HCQ based protocol: The clinical outcomes of the patients in terms of effectiveness are presented in light of conversion of results of NP swab for COVID-19 by day 14, and improvement in

symptoms by day 6 after using HCQ. The fever clinic was effective in managing the symptoms regardless of completion of HCQ. For example, on day 6, improvement of cough was achieved by more than 85% in all patients and fever was resolved in more than 83% of all patients. Regarding conversions of the results of the swab by day 14, no statistically significant difference existed between patients with confirmed COVID-19 who completed the course of HCQ and those who did not (p=0.34) [Table/Fig-4]. Similarly, there was no statistically difference in the resolution of fever by day 6 between those completed HCQ and those discontinued or did not started it. More specifically, 16.2% patients who took HCQ had fever compared with 9.5% of those who did not take HCQ (p=0.35). Similarly, there was no statistically significant difference for patients who completed HCQ and those who did not complete or start HCQ in terms of improvement of cough (p=0.18) [Table/Fig-4].

Variables	Completeness of HCQ course				**p-value
	Yes		No		
	n	(%)	n	(%)	
Swab result (n=49)					
Negative	23	(50)	1	(33.3)	0.34
Positive	23	(50)	2	(66.7)	
Fever (n=95)*					
No	62	(83.8)	19	(90.5)	0.35
Yes	12	(16.2)	2	(9.5)	
Cough (n=95)*					
Improved	70	(94.6)	18	(85.7)	0.18
Not improved	4	(5.4)	3	(14.3)	

[Table/Fig-4]: Conversion of results of Nasopharyngeal (NP) swab for COVID-19 by day 14 and improvement in symptoms by day 6 after using HCQ among responded participants.
*13 out of 108 lost to follow-up; **Chi-square test

Safety outcomes during the treatment at the fever clinic with HCQ based protocol: [Table/Fig-5] demonstrates the findings regarding safety of HCQ. Only 1.4% of those who took HCQ reported of having nausea compared to 16.7% patients who did not complete HCQ (p=0.69). Likewise, 9.5% of the patients using HCQ complained of headache as opposed to 9.1% of their counterparts, however, the results were not statistically significant (p=0.56). Furthermore, while 4.8% of the patients using HCQ complained of gastric upset, 4.1% of the patients who did not use or start HCQ with insignificant differences (p=0.64). None of the patients using HCQ showed abnormal findings on ECG including prolonged QTc interval or any other abnormal finding by day 3. While investigating the proportion of patients who discontinued HCQ, it was found that among the majority, 17.6% of the patients discontinued as advised by doctor other than the treating one, while 23.5% stopped on their own after negative results [Table/Fig-5].

Variables	HCQ				p-value
	Completed		Not completed		
	n	%	n	%	
Day 6 Nausea (n=95)#					
No	70	98.6	20	83.3	0.69
Yes	1	1.4	4	16.7	
Day 6 Headache (n=95)#					
No	19	90.5	68	91.9	0.56
Yes	2	9.5	6	9.1	
Day 6 Gastric upset (n=95)#					
No	20	95.2	71	95.9	0.64
Yes	1	4.8	3	4.1	
Day 3 ECG (n=97)*					
Not done	8	34.8	15	20.3	0.15
Normal	15	65.2	59	79.7	

Reason to discontinue HCQ (n=34)	n	%
Stopped by another doctor	6	17.6
Gastritis	1	2.9
Electrolytes disturbances	3	8.8
Self-stopped after negative swab results	8	23.5
Self-stopped after positive swab result	1	2.9
Drug-Drug interaction	1	2.9
Intolerance	1	2.9
Not improved	1	2.9
Other	12	35.2

[Table/Fig-5]: Adverse events reported after using HCQ to assess the safety of HCQ (n=108).
*11 out of 108 lost to follow-up; #13 out of 108 lost to follow-up; NA: Not applicable

DISCUSSION

This study was conducted to report the experience of implementing a fever clinic to manage the suspected and confirmed COVID-19 patients during the initial phase of the pandemic in Saudi Arabia. During early 2020, the clinical protocol approved by Saudi MoH included managing the patients in fever clinics using HCQ, besides supportive treatment in adults with mild and moderate symptoms Coronavirus Disease-2019 [23]. The study findings revealed that the concept of fever clinics was useful for managing suspected and confirmed cases. In particular, these clinics helped in providing better health services and ensured appropriate supportive management and close follow-up especially during the uncertain time of the pandemic where no effective treatment was proven or available. This is evident by the resolution of the symptoms for the vast majority of patients. At the same time, there were no additional benefits of HCQ compared to the supportive treatment in the study. More specifically, there was no statistically significant effect of HCQ in converting the NP swab from positive at the first visit to negative at the follow-up visits. Similarly, there was no significant additional improvement in alleviating symptoms such as fever and cough. The safety of HCQ was assessed by evaluating the symptoms such as nausea, headache, gastric upset and repeated ECG after giving HCQ to the patients. The findings showed that HCQ was tolerable by the patients with a very minimum reported side effects. Thus, HCQ was not found to be unsafe for the patients in this study especially when used as part of an approved protocol in mild to moderate COVID-19 patients based on clear eligibility criteria. These findings need to be interpreted in the sociocultural and demographic context of Saudi Arabia.

When compared with the existing literature, the findings of this study are consistent with the published studies elsewhere. For instance, similar to this study, Chen Z et al., (preprint) did not find any statistically significant difference for virological cure between intervention (HCQ) and control arm [24]. Likewise, Mallat J et al., (preprint), conducted a comparative observational study using data collected from routine care from four French tertiary care centres providing care to patients with COVID-19. It did not support HCQ use in patients admitted to hospital with COVID-19 who required oxygen, as there was no effect of HCQ in patients with COVID-19 [25].

Similarly, the study conducted by Boulware DR et al., revealed that HCQ did not have additional benefits in alleviating the symptoms associated with COVID-19 when initiated within 4 days, thus, illustrating compatible results with this study [26]. Moreover, findings from another study conducted on patients with mild to moderate COVID-19 disease were similar to findings of this study. More specifically, the results showed that HCQ was associated with a slower viral clearance at day 14 in COVID-19 patients with mild to moderate disease, and with no marked in improvement of inflammatory markers or lymphopenia rate [27]. Lastly, findings from a recently conducted systematic review ant meta-analysis revealed that there was no difference in virologic cure, safety or alleviation of symptoms of COVID-19 disease in patients with and without HCQ [28].

Regarding safety of HCQ, it was found in the current study that around more than a quarter of the patients discontinued the treatment on physician's advice and similar proportion stopped medication after having negative results for the swab. When comparing the findings with other studies in literature in terms of safety, the findings are almost similar. For instance, the study conducted by Chen J et al., revealed that 26.7% of the HCQ group and 20% of the participants in the control group complained of diarrhoea and altered liver function [29]. Similarly, the study by Chen Z et al., demonstrated that two patients in the HCQ arm showed mild adverse reactions such as rash, and headache [24]. Gautret P et al., showed that one patient discontinued treatment on day 3 because of nausea [17]. Similarly, Boulware DR et al., noticed more side effects with HCQ than with the control group, however, no serious adverse reactions were noticed in their study [26]. Additionally, a cross-sectional study conducted in Saudi Arabia to assess the safety of HCQ-based protocol, showed that 8.8% of patients discontinued the treatment because of the development of side effects, mainly cardiovascular adverse events (2.5%), followed by Gastrointestinal (GI) symptoms (2.4%) [30]. The results, coupled with the literature finding, provide the guidance that the use of HCQ needs to be based on strict eligibility criteria with appropriate monitoring and patient counseling.

The findings from this study and their comparison with other studies illustrate that there is no solid evidence to use HCQ among COVID-19 patients to reduce the morbidity and mortality. Also, HCQ need to be used cautiously in such patients. The differences and conflict of results in literature about efficacy and safety of HCQ in literature especially at the initial phase of the pandemic could be due to several reasons such as dosage of HCQ, time duration of HCQ, differences in the outcomes measured by different studies, severity of the COVID-19 patients, and also the sample size and method of assigning HCQ to the COVID-19 patients. Another possible reason could be differences in the eligibility criteria between the studies.

This is one of the first study in Saudi Arabia to document the experience of fever clinics established in the initial months of the COVID-19 pandemic with comments on the safety and efficacy of HCQ in Saudi population. Secondly, the investigators measured the viral load using standard PCR techniques and they also evaluated patients for main symptoms, collected their necessary labs to have the data on important variables.

Limitation(s)

Firstly, the patients were not randomised to receive HCQ and any other treatment, therefore, could not control for unknown confounders. Secondly, the sample size was small, therefore, they might have missed the true effect of HCQ in the population, if there was any. Thirdly, the patients were not followed beyond 14 days and there is likelihood that HCQ might show its effects later. Also, the study did not consider side effects that may have developed later, as the study period was relatively short. Lastly, this study was conducted in a single primary centre therefore the findings might not be generalisable to other settings in Saudi Arabia or neighboring countries. Furthermore, viral load or cycle threshold (Ct) values from RT-PCR, as a proxy for the likelihood of clearance of the virus, was not done.

CONCLUSION(S)

This study documented the experience of implementing a fever clinic to manage the suspected and confirmed COVID-19 patients with mild to moderate symptoms during the initial phase of the pandemic in Saudi Arabia. The study findings revealed that the concept of fever clinics were useful for managing suspected and confirmed cases. In particular, these clinics helped in providing better health services and ensured appropriate supportive management and close follow-up especially during the uncertain time of the pandemic where no effective treatment was proven or available. This is evident by the resolution of the symptoms for the vast majority of patients. At the same time, there were no additional benefits of HCQ compared to the supportive treatment in this study.

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REFERENCES

[1] Chen Y, Liu Q, Guo D. Emerging coronaviruses: Genome structure, replication, and pathogenesis. J Med Virol. 2020;92(4):418-23.
[2] Tu H, Tu S, Gao S, Shao A, Sheng J. The epidemiological and clinical features of COVID-19 and lessons from this global infectious public health event. J Infect. 2020;81(1):01-09.
[3] Zhong BL, Luo W, Li HM, Zhang QQ, Liu XG, Li WT, et al. Knowledge, attitudes, and practices towards COVID-19 among Chinese residents during the rapid rise period of the COVID-19 outbreak: A quick online cross-sectional survey. International Journal of Biological Sciences. 2020;16(10):1745-52.
[4] Khurshid Z, Asiri FYI, Al Wadaani H. Human saliva: Non-invasive fluid for detecting Novel Coronavirus (2019-nCoV). Int J Environ Res Public Health. 2020;17(7):2225.
[5] Peng X, Xu X, Li Y, Cheng L, Zhou X, Ren B. Transmission routes of 2019-nCoV and controls in dental practice. International Journal of Oral Science. 2020;12(1):01-06.
[6] Team E. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19)—China, 2020. China CDC weekly. 2020;2(8):113.
[7] Kucharski AJ, Russell TW, Diamond C, Liu Y, Edmunds J, Funk S, et al. Early dynamics of transmission and control of COVID-19: A mathematical modelling study. The Lancet Infectious Diseases. 2020;20(5):553-58.
[8] Nishiura H, Jung SM, Linton NM, Kinoshita R, Yang Y, Hayashi K, et al. The extent of transmission of novel coronavirus in Wuhan, China, 2020. J Clin Med. 2020;9(2):330.
[9] Khachfe HH, Chahrour M, Sammouri J, Salhab H, Makki BE, Fares M. An epidemiological study on COVID-19: A rapidly spreading disease. Cureus. 2020;12(3):e7313.
[10] Peeri NC, Shrestha N, Rahman MS, Zaki R, Tan Z, Bibi S, et al. The SARS, MERS and novel coronavirus (COVID-19) epidemics, the newest and biggest global health threats: What lessons have we learned? International Journal of Epidemiology. 2020;49(3):717-26.
[11] Li H, Liu SM, Yu XH, Tang SL, Tang CK. Coronavirus disease 2019 (COVID-19): Current status and future perspectives. International Journal of Antimicrobial Agents. 2020;55(5):105951.
[12] Ministry of Health SA. Fever clinics 2020 [10 October 2021]. Available from: https://www.moh.gov.sa/en/HealthAwareness/Tatamman-Clinics/Pages/default.aspx.
[13] Colson P, Rolain JM, Lagier JC, Brouqui P, Raoult D. Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. Int J Antimicrob Agents. 2020;2020:105932(10.1016).
[14] Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. N Engl J Med. 2020;382:1787-99.
[15] Mehra MR, Desai SS, Ruschitzka F, Patel AN. Retracted: Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: A multinational registry analysis. Elsevier; 2020.
[16] Cavalcanti AB, Zampieri FG, Azevedo LC, Rosa RG, Avezum A, Veiga VC, et al. Hydroxychloroquine alone or in combination with azithromycin to prevent major clinical events in hospitalised patients with coronavirus infection (COVID-19): Rationale and design of a randomised, controlled clinical trial. medRxiv. 2020.
[17] Gautret P, Lagier JC, Parola P, Meddeb L, Mailhe M, Doudier B, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: Results of an open-label non-randomized clinical trial. International Journal of Antimicrobial Agents. 2020;56(1):105949.
[18] Molina JM, Delaugerre C, Le Goff J, Mela-Lima B, Ponscarme D, Goldwirt L, et al. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. Medecine et Maladies Infectieuses. 2020;50(4):384.
[19] Dyall J, Gross R, Kindrachuk J, Johnson RF, Olinger GG, Hensley LE, et al. Middle East respiratory syndrome and severe acute respiratory syndrome: Current therapeutic options and potential targets for novel therapies. Drugs. 2017;77:1935-66.
[20] Expert consensus on chloroquine phosphate for the treatment of novel coronavirus pneumonia. 2020. Available from: https://pubmed.ncbi.nlm.nih.gov/32075365/.
[21] Tang W, Cao Z, Han M, Wang Z, Chen J, Sun W, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: Open label, randomised controlled trial. BMJ. 2020;369.
[22] Hernandez AV, Roman YM, Pasupuleti V, Barboza JJ, White CM. Hydroxychloroquine or chloroquine for treatment or prophylaxis of COVID-19: A living systematic review. Annals of Internal Medicine. 2020;173(4):287-96.
[23] Ministry of Health SA. Supportive care and antiviral treatment of suspected or confirmed COVID-19 infection verion 1.4 (April 2020) 2020. Available from: http://omranhospital.net/wp-content/uploads/2020/05/MoH-COVID-19-Protocol-V1.463931.pdf-1.pdf.
[24] Chen Z, Hu J, Zhang Z, Jiang S, Han S, Yan D, et al. Efficacy of hydroxychloroquine in patients with COVID-19: Results of a randomized clinical trial. medrxiv. 2020.
[25] Mallat J, Hamed F, Balkis M, Mohamed MA, Mooty M, Malik A, et al. Hydroxychloroquine is associated with slower viral clearance in clinical COVID-19 patients with mild to moderate disease: A retrospective study. MedRxiv. 2020.
[26] Boulware DR, Pullen MF, Bangdiwala AS, Pastick KA, Lofgren SM, Okafor EC, et al. A randomized trial of hydroxychloroquine as postexposure prophylaxis for Covid-19. New England Journal of Medicine. 2020;383(6):517-25.

[27] Rosenberg ES, Dufort EM, Udo T, Wilberschied LA, Kumar J, Tesoriero J, et al. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York State. JAMA. 2020;323(24):2493-502.
[28] Sarma P, Kaur H, Kumar H, Mahendru D, Avti P, Bhattacharyya A, et al. Virological and clinical cure in COVID-19 patients treated with hydroxychloroquine: A systematic review and meta-analysis. Journal of Medical Virology. 2020;92(7):776-85.
[29] Chen J, Liu D, Liu L, Liu P, Xu Q, Xia L, et al. A pilot study of hydroxychloroquine in treatment of patients with moderate COVID-19. Zhejiang da xue xue bao Yi xue ban = Journal of Zhejiang University Medical sciences. 2020;49(2):215-19.
[30] Mohana A, Sulaiman T, Mahmoud N, Hassanein M, Alfaifi A, Alenazi E, et al. Hydroxychloroquine safety outcome with an approved therapeutic protocol for COVID-19 outpatients in Saudi Arabia. International Journal of Infectious Diseases. 2021;102:110-14.

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