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Original Article

Is Immunomodulatory Property of Hydroxychloroquine Beneficial for Severe COVID-19? A Hospital Based Retrospective Observational Study

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ABSTRACT

Since the beginning of the COVID-19 pandemic, Hydroxychloroquine is being prescribed by the doctors all over the world for the treatment as well as prevention of COVID-19 with varying results. As we know damage in severe COVID-19 disease occurs mainly via the immunological mechanism. There is an assumption that HCQ has immunomodulatory property and thus may have a beneficial role in severe COVID-19 disease. In this retrospective study, we describe our experience of using low dose of HCQ (200mg/day) in 27 hospitalized severe cases of COVID-19 disease. We found, though the use of HCQ resulted in improvements in chest X-rays, there was no significant reduction in the deaths in the cases where HCQ was used.

INTRODUCTION

Our Hospital is a 100 bedded COVID-19 Hospital with 10 ICU beds in Keonjhar, Odisha set up especially in light of the COVID-19 pandemic by the Government during April 2020.

Hydroxychloroquine (HCQ) is an aminoquinoline, which is chloroquine with one of its N-Ethyl Group Hydroxylated at position two. It was originally developed as an anti-malarial. But now it is mainly used as an immunosuppressive agent in auto-immune diseases such as Systemic Lupus Erythematosus (SLE) and Rheumatoid Arthritis. During the SARS Cov-1 outbreak, HCQ was found to have in-vitro activity against the virus. So when SARS Cov-2 or COVID-19 pandemic began, scientists hoped that HCQ may act as an antiviral against the new virus [1]. Indian Council of Medical Research (ICMR) recommended HCQ for prophylaxis as well as treatment for COVID-19 [2]. In the USA, Emergency Use Authorization (EUA) was issued by USFDA to allow the use of HCQ in COVID-19, which was revoked later [3].

Large numbers of clinical trials were started in different countries to study the safety and efficacy of HCQ in COVID-19. Initial pilot study on HCQ was done in China, which was inconclusive [4]. The study done by Geleris et al in the USA did not find any significant effect of HCQ on COVID-19 mortality in hospitalized patients [5]. However, a study in France reported a significant decrease in viral load following the use of HCQ, though the study brought up many controversies later [6]. But again two multi-centric international trials (Solidarity and RECOVERY) found that HCQ did not improve outcomes [7, 8]. Another study from Belgium found low dose HCQ was associated with lower mortality in hospitalized COVID-19 patients [9]. Of interest were the patients with Rheumatoid Arthritis and SLE, who received long-term low dose HCQ, though they were not protected from the infection, but had significantly less mortality from the COVID-19 disease [10, 11]. At a lower dose HCQ may act as an immunomodulatory agent, which may be protective against the inflammatory damage brought about by SARS Cov-2 in the pulmonary phase of the disease [12, 13].

This study was undertaken to find out if use of HCQ in the pulmonary phase help modify the disease process beneficially for severe COVID-19 patients.

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MATERIALS & METHODS

This is a retrospective observational study. We studied all the case records of severe cases of COVID-19 admitted to our hospital between April 2020 and December 2020. A severe case was defined as "Oxygen Saturation dropping less than 90 % in room air at admission or at any time later during the period of hospitalization" [14]. Among the severe cases, we did not include critical cases such as ARDS (Acute Respiratory Distress Syndrome) and Septic Shock. We searched cases where HCQ was used in the pulmonary phase at least for seven days among these severe cases of COVID-19.

Our hospital started using HCQ after a chance observation of improvement in one case of severe COVID-19 disease following the use of HCQ. On 15th October 2020, the Institutional Ethics Committee and Expert COVID-19 Committee of our hospital approved the use of HCQ in those severe COVID-19 patients, who failed to improve after one week of standard treatment.

The severe cases were treated as per the "Severe COVID-19 Protocol" as laid down by the health and family welfare department of the Government of India [14]. The cases, which did not improve after 1 week of the above prescribed treatment, who had no known contraindications for the use of HCQ and were able to take orally, were started with low dose HCQ, i.e.; 400mg on the first day as loading dose followed by 200mg once daily orally for seven days or beyond. This dose was adopted from the usual low dose regime of HCQ in Rheumatoid Arthritis, which was safe as well as effective as an immunomodulatory agent [15].

We noted the vital signs, oxygen requirements, use of Non-Invasive Ventilation (NIV) and chest X-rays of these patients on the day of starting HCQ and again after seven days, from the case records. We used the RALE (Radiographic Assessment of Lung Edema) score to describe Chest X-rays and to add objectivity to our observation [16]. We also looked for any arrhythmias, gastrointestinal disturbances, vision or nervous system abnormalities, and ECG changes in these patients while receiving HCQ [17]. We further noted whether the patient was discharged or expired at the end.

Further, we took age and sex matched controls of severe COVID-19 cases from the severe COVID-19 patients treated before 15th October 2020. To eliminate the confounding factors, we made the common co-morbidities comparable in the two groups. Then we compared the death rates in these the two groups. We also compared the use of NIV and chest X-ray RALE scores after two weeks of hospitalization in the survivors (corresponding to one week after treatment with HCQ in the study group).

Statistical analysis was done using the web-based software Medcalc [18].

RESULTS

The Hospital started functioning on 20th April 2020 and the first COVID-19 positive case was admitted on 23rd May 2020. There were total 2033 admissions with 76 deaths in our hospital by 31st December 2020. Total Severe Cases were 327. There were 27 patients, who received HCQ for seven days or more. Age and sex matched controls were taken from the rest of the severe COVID-19 cases where HCQ was not used and were similar in their co-morbidities.

Table 1 describes the 27 severe COVID-19 cases, who received HCQ for minimum of seven days. The youngest patient was 21 years and the eldest patient was 84 years. However, most patients were between the ages of 40 to 60 years in this study. Males far outnumbered the females (85.1%). Out of the 27 cases, 10(37%) patients had Type 2 Diabetes Mellitus (DM-2), seven (25.9%) had Hypertension ((HTN) and eight (29.6%) had Obesity (BMI>30). Total 21(77.7%) patients were discharged and six (22.2%) patients expired.

Table 2 describes the features of the 27 age and sex matched controls, taken out of the severe COVID-19 patients, who did not receive HCQ. The youngest patient was 24 years and the eldest patient was 82 years. Out of the 27 controls, Nine (33.3%) patients had Type 2 Diabetes Mellitus (DM-2), 10 (37%) had Hypertension ((HTN) and nine (33.3%) had Obesity (BMI>30). About 70.4% (19) patients were discharged and eight (26.9%) patients expired.

Table 3 compares the chest X-ray RALE scores of the cases before and after giving low dose HCQ for one week. The mean Chest X-ray RALE scores decreased from 20.71 to 12.57 after the therapy (P-value = 0.0069).

Table 4 compares chest X-ray RALE scores and use of NIV among the cases and controls. The mean RALE score was 12.57 in the study group whereas the same was 22.11 in the control group (P= 0.0004). Regarding NIV use, 10 patients (37%) in the study group and 14 patients (51.8%) in the control groups were requiring NIV after 2 weeks (P= 0.278, which is statistically not significant).

There were co-morbidities in the form of Diabetes, Hypertension and Obesity in the case and control groups and their proportions were not significantly different (P values 0.7779, 0.3842, and 0.7718 respectively).

We compared the proportions of deaths in the two groups, the 95% confidence interval was -17.9580% to 26.7859% and the P value 0.6910, which was statistically not significant.

We looked for any adverse reactions or side effects related to use of HCQ in the study group and we did not found any such events recorded.

DISCUSSION

Though the chest X-ray RALE scores decreased significantly after the use of HCQ in the study group compared to controls, HCQ has no effect on the outcome of severe COVID-19 cases. The difference of death or NIV use was not significantly different in the case and control group.

There have been many studies that have found HCQ to be effective in the management of COVID-19. Catteau et al from Belgium and Monforte et al from Milan, Italy found the use of HCQ reduced the death rate in the hospitalized COVID-19 patients [9, 19]. Derwand et al from Germany found that when COVID -19 outpatients were given low dose HCQ along with Zinc and Azithromycin for five days, there were fewer deaths and hospitalizations in the treatment

Table 1. Cases of evere COVID-19, who received seven days of HCQ

Age(years)	Male	Female	DM-2	HTN	OBESITY	DISCHARGE	DEATH
<40	5	0	0	0	1	5	0
40-60	11	1	7	5	5	9	3
>60	7	3	3	2	2	7	3
Total	23	4	10	7	8	21	6

Table 2. Age and sex matched controls of severe COVID-19 patients who did not received HCQ

Age(years)	Male	Female	DM-2	HTN	OBESITY	DISCHARGE	DEATH
<40	5	0	0	0	2	4	1
40-60	11	1	4	5	4	9	3
>60	7	3	5	5	3	6	4
Total	23	4	9	10	9	19	8

Table 3. Comparison of Chest X-ray RALE Scores of severe COVID-19 cases before and after receiving HCQ

Parameters	Mean RALE Score in Chest X-ray
Before HCQ	20.7 1 (SD 10.36) n=27
After HCQ	12.57 (SD 10.91) N=27
95% CI	-13.95 to -2.32
P Value	0.0069

Table 4. Comparison of Chest X-ray RALE Scores and use of NIV in cases and controls after two weeks of hospitalization

Parameters	Mean RALE Score in Chest X-ray after 2 weeks of admission	NIV use after 2 weeks of admission
Cases	12.57 (SD 10.91) N=27	10(37%)
Controls	22.11 (SD 7.41)	14(51.8%)
95% CI	4.44 to 14.63	-11.08 to 38.10
P Value	0.0004	0.278

group in comparison to the control group [20]. As we know, the pulmonary phase of COVID-19 involves the release of interleukins and other inflammatory mediators and influx of inflammatory cells leading to cell damage [21]. HCQ may act as an immunomodulatory agent at a low dosage and can inhibit the production of cytokines such as IL-1, IL-2, IL-6, IL-17, and IL-22 as well as interferons and tumor necrosis factors (TNF) and thus is a potent inhibitor of cytokine storm [22]. HCQ may also have an antithrombotic effect in addition to its immunomodulatory property [23].

However, there are many studies where the results have not been so encouraging. Results of the two well known studies (Solidarity and RECOVERY trials) have found HCQ to be ineffective [7, 8]. Pathak et al did a meta-analysis of seven studies that also showed no evidence of benefit. However these studies included negative RTPCR as the outcome. Also HCQ was used in higher dosage (800 mg per day) in these studies [24].

Our study has several drawbacks as well. The sample size is very small to draw any conclusion out of this study. Besides observational and retrospective studies have their own limitations. However, this study may be seen as a step for further pursuance of the truth and should encourage further randomized control trials on this topic.

Another concern always has been the toxicity and side effects of HCQ. Though HCQ has been proved to be safe in malaria and autoimmune diseases, patients with severe COVID-19 are usually aged and with co-morbidities such as diabetes and cardiovascular diseases. Also, severe COVID-19 patients may have altered metabolism, which can contribute to the side effects of HCQ [17].. However we did not encounter any features of an adverse effect of HCQ in our study. We infer that low dose HCQ at 200 mg per day is quite safe and well-tolerated. In the end, although promising results have been shown by the use of HCQ in patients with COVID-19, our observations need to be further tested with larger studies and Randomised Control Trials (RCT). Till then, it will be wise to remain cautious while using HCQ in COVID-19 [25, 26].

CONCLUSIONS

Low-dose HCQ (400 mg on the first day followed by 200 mg once daily) in the pulmonary phase of severe COVID-19 disease was not associated with reduction in the death rates. HCQ at this dose appears to be safe in severe COVID-19. Although this study shows no beneficial role of HCQ in severe COVID-19 disease, further studies with larger number of subjects and RCTs (Randomized Controlled Trials) may find out positive results.

REFERENCES

1. Keyaerts E, Vijgen L, Maes P, Neyts J, Ranst M Van: In vitro inhibition of severe acute respiratory syndrome

coronavirus by chloroquine. Biochem Biophys Res Commun. 2004, 323:264-8. doi:10.1016/j.bbrc.2004.08.085
2. Nina PB, Dash AP: Hydroxychloroquine as prophylaxis or treatment for COVID-19: What does the evidence say? Indian J Public Health. 2020, 64:125-127. doi:10.4103/ijph.IJPH_496_20
3. Thomson K, Nachlis H. : Emergency use authorizations during the COVID-19 pandemic: lessons from hydroxychloroquine for vaccine authorization and approval. JAMA. 2020, 324:1282-1283. doi:10.1001/jama.2020.16253
4. Chen J, Liu D, Liu L, et al.: A pilot study of hydroxychloroquine in treatment of patients with moderate COVID-19. J Zhejiang Univ . 2020, 49:215-219. 10.3785/j.issn. doi:1008-9292.2020.03.03
5. Geleris J, Sun Y, Platt J, et al.: Observational study of hydroxychloroquine in hospitalized patients with Covid-19. N Engl J Med. 2020, 382:2411-8. 10. doi:1056/NEJMoa2012410
6. 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 , 56:105949. doi:10.1016%2Fj.ijantimicag.2020.105949
7. WHO: "Solidarity" clinical trial for COVID 19 treatments. (2020). Accessed: January 22, 2021: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solida
8. University of Oxford: The RECOVERY Trial. (2020). Accessed: November 1, 2020: https://www.recoverytrial.net/files/recovery_dexamethasone_statement_160620_v2final.pdf
9. Catteau L, Dauby N, Montourcy M, et al.: Low-dose hydroxychloroquine therapy and mortality in hospitalised patients with Covid- 19: a nationwide observational study of 8075 participants. Int J Antimicrob Agents. 2020, 56:106144. doi:10.1016/j.ijantimicag.2020.106144
10. Gentry CA, Humphrey MB, Thind SK, Hendrickson SC, Kurdgelashvili G, Williams RJ: Long-term hydroxychloroquine use in patients with rheumatic conditions and development of SARS-CoV-2 infection: a retrospective cohort study. Lancet Rheumatol. 2020, 2:689-97. doi:10.1016/S2665-9913(20)30305-2
11. Bénézit F, Le Bot A, Jouneau S, et al.: COVID-19 in Patient with Sarcoidosis receiving long term hydroxychloroquine treatment, France, 2020. Emerg Infect Dis. 2020 , 26:2513-2515. doi:10.3201/eid2610.201816
12. Li X, Wang Y, Agostinis P, Rabson A, Melino G, Carafoli E, Shi Y & Sun E: Is hydroxychloroquine beneficial for COVID-19 patients?. Cell Death Dis . 2020, 11:512. doi:10.1038/s41419-020-2721-8
13. Chandler L C, Yusuf IH, McClements M E, Barnard AR, MacLaren RE and Xue K: Immunomodulatory effects of hydroxychloroquine and chloroquine in viral infections and their potential application in retinal gene therapy. Int. J. Mol. Sci. 2020, 21(14):4972. doi:10.3390/ijms21144972
14. Government of India, Ministry of Health and Family Welfare: CLINICAL MANAGEMENT PROTOCOL: COVID-19. (2020). Accessed November11,2020: https://www.mohfw.gov.in/pdf/UpdatedClinicalManagementProtocolforCOVID19dated03072020.pdf
15. Pavelka K, Sen KP, Pelísková Z, et al Hydroxychloroquine sulphate in the treatment of rheumatoid arthritis: a double blind comparison of two dose regimens. Annals of the Rheumatic Diseases 1989;**48:**542-546. doi:10.1136/ard.48.7.542
16. Warren MA, Zhao Z, Koyama T, et al.: Severity scoring of lung edema on the chest radiograph is associated with clinical outcomes in ARDS. Thorax. 2018 , 73:840-846. doi:10.1136/thoraxjnl-2017-211280
17. Gevers S, Kwa M.S.G. Kwa, Wijnans E., Nieuwkoop C Van: Safety considerations for chloroquine and hydroxychloroquine in the treatment of COVID-19. Clin. Microbiol. Infect.. 2020, 26:1276-1277. doi:10.1016/j.cmi.2020.05.006.
18. MEDCALC: Statistical Software. (2019). Accessed: December 29, 2020: https://www.medcalc.org/
19. Monforte A , Tavelli A, Bai F, Marchett G: Effectiveness of hydroxychloroquine in Covid-19 disease: a done and dusted deal?. Int J Infect Dis. 2020, 99:75-76. doi:10.1016/j.ijid.2020.07.056
20. Derwand R, Scholz M, Zelenko V: COVID-19 outpatients - early risk-stratified treatment with zinc plus low dose hydroxychloroquine and azithromycin: a retrospective case series study. Int J Antimicrob Agents . 2020, 56:106214. doi:10.1016/j.ijantimicag.2020.106214
21. Parasher A: COVID- 19: Current understanding of its pathophysiology, clinical presentation, and treatment. Postgrad Med J. 2020, Published Online First:September 25. doi: 10.1136/postgradmedj-2020-138577
22. Richard SA , Kampo S, Hechavarria ME, Sackey M, Buunaaim ADB, Kuugbee ED, and Anabah TW: Elucidating the pivotal immunomodulatory and anti-Inflammatory potentials of chloroquine and hydroxychloroquine. J Immunol Res. 2020, 2020:4582612. doi:10.1155/2020/4582612
23. Roldan EQ, Biasiotto G, Magroa P, Zanella I: The possible mechanisms of action of 4-aminoquinolines (chloroquine/hydroxychloroquine) against Sars-Cov-2 infection (COVID- 19): a role for iron homeostasis?. Pharmacol Res. 2020, 158:104904. doi:10.1016/j.phrs.2020.104904
24. Pathak SK, Salunke AA, Thivari P, et al.: No benefit of hydroxychloroquine in COVID- 19: results of systematic review and meta-analysis of randomized controlled trials. Diabetes Metab Syndr. 2020, 14:1673-1680. doi:/10.1016/j.dsx.2020.08.033
25. Ferner RE, Jeffrey K JK: Chloroquine and hydroxychloroquine in covid-19. BMJ. 2020 , 369:m1432. doi:10.1136/bmj.m1432
26. Schluger NW: The Saga of hydroxychloroquine and Covid-19: a cautionary tale. Ann Intern Med. 2020, 173:662-663. doi:10.7326/M20-5041