Clearing the fog: Is Hydroxychloroquine effective in reducing Corona virus disease 2019 progression: A randomized controlled trial

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Study design, setting and participants: This single Centre, parallel open label randomized controlled trial was carried out during 10th April to 31st May 2020 at department of Pulmonology, Pakistan Emirates Military Hospital (PEMH) over 500 patients from both genders between 18-80 years of age. The study design was approved by institutional ethical review committee. The study population was comprised of patients from both genders with Mild confirmed COVID-19 after their written consent. The study protocol and approval documents are available online at ClinicalTrials.gov with trial number of NCT04491994.

Sample size calculation: Sample size was calculated using OPEN EPI with 5% level of Confidence and 80% power to detect a difference and enrolment ration 2:1 between intervention and control group, at a two-sided significance level of α=0.05, of 7 days in the median time to clinical improvement between the two groups, assuming that the median time in the SOC group was 14 days and assuming 55% efficacy of HCQ in preventing disease progression and achieving viral clearance at day 7. Calculated sample size was 467, however we used a sample size of 500.

Enrolment procedure: During study period, 672 confirmed PCR positive cases were assessed for eligibility. 132 did not meet selection criteria and subsequently excluded. 540 patients were then enrolled and randomized. Further 20 patients were excluded from analysis as 15 withdrew consent and 5 became symptomatic before first dose of HCQ. During follow up 13 patients were found to be deviated from advised therapy and 7 were lost to follow up yielding a final study population of

500. **Figure 1** summarizes this process. Randomization rules were designed by Dr. Wasim Alamgir together with principal investigators and implemented by an independent statistician who was not involved in data analysis. Stratified random sampling was applied to stratify all eligible patients according to age, gender and comorbidities. Computerized random number generator was used and allocation was done in 2:1 sequence. Cards with each group assignment number randomly generated by computer were placed in sequentially numbered envelopes that were opened as the patients were enrolled

Interventions: A total of 349 patients included in intervention group and 151 in control group. In Hospital, HCQ was given to patients after written consent and after considering its contraindications. Three hundred and forty-nine (349) patients were included in intervention group and given HCQ in addition to standard of care treatment. After 12 hours of randomization HCQ was given. Standard dose of HCQ was 400 mg by mouth twice a day for day one followed by 200 mg 12 hourly for next 5 days. The patients who did not give consent for treatment with HCQ or had a known allergy to HCQ or chloroquine or had another known contraindication to treatment with the study drug, including retinopathy, G6PD deficiency and QT prolongation served as controls. Controls were matched with participants on the basis of age, gender and co morbids and comprised of 151 patients. Standard of care (SOC) treatment comprised of daily oral Vit C (2gms), oral Zinc (50mg), oral Vit-D (alfacalcidol 1ug) and tablet Paracetamol (for body aches/fever), intravenous fluids, hemodynamic monitoring, and laboratory testing for SARS-CoV-2 and baseline blood parameters. Neither patients, nor investigators, nor statisticians were masked to treatment assignment. Lab staff who performed sampling for PCR, basic blood tests and other routine measurement were unaware of treatment information. Data regarding age, co-morbidities, history of contact with a positive patient, days since contact, duration of symptoms, PCR status

with date and base line labs/X-ray chest were recorded. Any patient with day 0 CRP greater than 6mg/dl, Absolute lymphocyte count (ALC) < 1000 or evidence of infiltrates on X-ray chest were excluded. Daily temperature, respiratory rate (RR) and resting O2 saturation with pulse oximetry were monitored in all patients during their hospitalization.

Operational definitions: A case was considered confirmed on the basis of positivity of RT-PCR of combined Oropharyngeal and Nasopharyngeal swabs. Severity of disease was defined as per criteria designed by WHO[11]. Mild disease meant Patients with uncomplicated upper respiratory tract viral infection having non-specific symptoms such as low-grade fever (fever < 100F for < 3 days), fatigue, body aches, cough (with or without sputum production), anorexia, muscle pain, sore throat, nasal congestion, anosmia, headache and rarely diarrhea, nausea, and vomiting. PCR sampling was done on day 7 and 14 of admission. Any chronic health condition for which patients were on prior treatment was considered as co morbidity. After start of treatment, development of fever > 101 F for > 72 hours, shortness of breath by minimal exertion (10-Step walk test), derangement of basic lab parameters (ALC < 1000 or raised CRP) or appearance of infiltrates on CXR during course of treatment was labeled as progression irrespective of PCR status. PCR status of patients was checked after 7 days and 14 days of initiation of treatment.

Inclusion and exclusion criteria: Inclusion criteria included (1) Mild Corona virus disease (COVID-19) (2) PCR confirmed infection (3) Hospital admitted patients (4) 18-80 years age Exclusion criteria were (1) Moderate, severe and critical COVID-19 (2) day 0 CRP greater than 6mg/dl, ALC < 1000 or evidence of infiltrates on X-ray chest (3) comorbidity with life expectancy less than 6 months (4) Contraindications to HCQ therapy.

Outcomes: Primary outcome was disease progression within 5 days of start of treatment. This was defined by development of fever > 101 F for > 72 hours, shortness of breath by minimal exertion

(10- Step walk test), derangement of basic lab parameters (ALC < 1000 or raised CRP) or appearance of infiltrates on CXR. Patients underwent 6 hourly axillary temperature check, daily 10 feet walk test, daily Blood counts, CRP and X-Rays on day 0, 3 and 5.

Secondary outcome was Viral clearance. PCR negativity on day 7 and 14 after admission was recorded.

Statistical analysis: Statistical interpretation of data was performed using Statistical Package for Social Sciences (SPSS) version 23. Results were expressed as mean, standard deviation (±SD) for all continuous variables and frequency and percentage for categorical data. We used t-test and chi-square test as appropriate to the nature and distribution of the variables. A p-value < 0.05 was considered statistically significant.