Ventricular Arrhythmia Risk Based on Ethnicity in COVID-19 Patients on Hydroxychloroquine and Azithromycin Combination: Viewpoint

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Abstract

There are many reports available now, which are mostly observational or registry trial outcomes having varied results on coronavirus 2019 (COVID-19) patients put on hydroxychloroquine and azithromycin combination. Some are showing increased in-hospital mortality and ventricular arrhythmia increase, while some are showing overall benefit with significant viral RNA load reduction. Everyday things are getting more complicated with the publication of these different outcomes. This needs to be addressed.

Keywords COVID-19 · Ventricular arrhythmia · Cardiac arrhythmia · Asian · Hydroxychloroquine · Azithromycin

Introduction

Coronaviruses are positive-stranded RNA viruses which are enveloped and their envelope fused with host cell membrane with the spike glycoprotein (S) mediating the virus entry into cell [1]. There have been reports of efficient in vitro inhibition of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) with drugs remdesivir (GS-5734) and chloroquine (CQ) phosphate [2]. A recent study by Mehra et al. [3] has shown hydroxychloroquine, hydroxychloroquine with a macrolide, chloroquine, and chloroquine with a macrolide all increased in-hospital mortality as well as de novo ventricular arrhythmia during hospitalization although Asians consisted only 7.9% of the total study population. In this study, it was interesting to find that the Asian population benefited from the combinations with a hazard ratio and 95% CI of 0.717 (0.668–0.769), showing a decrease in in-hospital mortality. Soon after the publication, this study has received a sharp criticism from all over the world regarding their design of sample collection and many other issues [4], and a signed letter was forwarded to The Lancet regarding the concerns of the trial [5]. Just after this publication, the UK’s RECOVERY trial body [NCT04381936] went back to reassess their interim data of the safety of their ongoing trial drugs, which included HCQ, and found no safety concerns and hence did not stop the trial [6]. Based on the severe criticism, the article was soon retracted [7]. Reports have also shown that the risk is increased with the combination of two separate drugs, each of which can cause drug-induced QT prolongation leading to torsade de pointes (TdP) and subsequent ventricular arrhythmia (VA) [8].

A French study showed a significant benefit when HCQ was used in COVID-19 patients in reducing or even clearing SARS-CoV-2 viral RNA load in 6 days, and the addition of azithromycin reinforced the chances [9]. These conflicting results are creating massive confusion among the medical fraternity. Another retrospective multicenter cohort study involving 1438 hospitalized patients (mostly white) with COVID-19 showed no mortality benefit with the HCQ + AZ combination, but cardiac arrest was significantly higher in the combination group than with each drug alone [10]. Unfortunately, there are rare papers on this combination drug from the Asian subcontinent, and hence other publications are looked for where this combination was used. In a study on uncomplicated falciparum malaria from India, we found a significant improvement in clinical and parasitologic outcomes, combined with cure rates of almost 97%, but at the same time, there were no serious cardiac adverse outcomes [11]. Animal study in an anesthetized guinea pig showed that the combination of AZ with chloroquine did not have any added potential to cause...
arrhythmias [12]. Another study with two groups investigating the pharmacokinetic interaction with the combination of chloroquine and AZ did not find any clinically significant PK interaction [13]. It has been often seen that AZ causes cardiac arrhythmias mostly in aged, ill patients with many comorbidities and concomitant medications, which put them intrinsically to high CV risk groups [14]. The chances of prolongation of the QTc (corrected QT) interval and subsequent risk of torsade de pointes (TdP) with HCQ are found to be dose dependent where it is seen that the mean increases in QTc are 6.1 ms after a dose of 600 mg and 28 ms after a dose of 1200 mg [15].

**Clinical Studies and Cardiac Arrhythmias in COVID-19**

Sudden cardiac death (SCD) is seen in almost 40 cases per 100,000 persons per year in each country of Asia, which is lower than in Europe or the USA, where we find ranges from 50 to 100 per 100,000 persons per year [16]. The commonest fatal cascade in SCD appears to start with ventricular tachycardia (VT) degenerating first to ventricular fibrillation (VF) to SCD. Further complications have been reported due to virus-induced microthrombogenesis [21]. In critically ill patients of SARS-CoV-2 infection, thrombotic complications have been reported due to virus-induced endothelitis [22,23]. Pan et al. [24] suggested a few probable mechanisms of cardiac arrest in patients during the severe acute respiratory syndrome (SARS) outbreak, and that same concept is now being extrapolated to explain the arrhythmias in SARS-CoV-2. They share the view that (a) SARS-induced lung injury leads to hypoxemia and an altered, imbalanced state in myocardial electricity; (b) direct damage to the new myocardial cells and/or conduction system; (c) aggravation of pre-existing morbidities related to myocardium or conduction disturbances; and (d) endogenous catecholamine release owing to the severe anxiety in the patients that leads to further myocardial electrical instability.

In general, atrial fibrillation is a major predisposing factor to SCD, but in patients without AF, SCD, and VA, it increase consistently with age [25]. Ventricular fibrillation and ventricular tachycardia are reported in higher proportions with elevated troponin T levels [26]. The potential role of pharmacological interventions in causing prolongation of corrected QT (QTc) interval must be remembered as these drugs are now quite often used in these frail patients of COVID-19 and include the commonly used drugs hydroxychloroquine, azithromycin, and lopinavir/ritonavir. Antimalarial drugs like hydroxychloroquine have a direct effect on ventricular repolarization by blocking the KCNH2-encoded HERG/K,1.1 potassium channel and potentially prolonging the QTc [8]. The macrolide azithromycin also shares the same mechanism of blockade of the rapid component, IKr, of the delayed rectifier potassium current IK [27]. The cytokine storm seen in severe COVID-19 patients leads to acute respiratory distress syndrome (ARDS) by releasing many cytokines like interleukin (IL)-1B, IL-6, IL-12 and various chemokines [28], with IL-6, IL-1 modulating the expression and/or function of cardiac K+ and Ca++ channels, thereby causing prolongation of ventricular action potential duration, which finally predisposes to arrhythmias [29]. Tisdale et al. have created a Tisdale risk score for hospitalized patients to predict QTc > 500 msec [30]. This score, nowadays, is in routine use for COVID-19 patients starting HCQ, and it states that a risk score of ≤ 6 confers low risk, 7–10 medium risk, and ≥ 11 high risk of drug-associated QTc prolongation [30]. Drug-induced QT prolongation risk is around 6%, and out of that, 0.3% have a chance to develop TdP, and VA risk is seen in 2.6% and the risk to be increased when concomitant multiple QT-prolonging drugs are used [31].
| Trial number     | Primary end point                                                                 | Type of patient                                                                 | Status and type of study                                                                 |
|------------------|-----------------------------------------------------------------------------------|----------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|
| NCT04329832      | COVID Ordinal Outcomes Scale at 14 days                                           | Hospitalized patients with suspected or confirmed COVID-19                      | Recruiting phase 2: Experimental Arm, hydroxychloroquine; Active Comparator Arm, Azithromycin |
| NCT04334382      | Hospitalization within 14 days of enrolment                                       | Outpatients in Utah with COVID-19                                               | Recruiting phase 3: Experimental Arm, hydroxychloroquine; Active Comparator Arm, azithromycin |
| NCT04370782      | 1. Time to resolution of symptoms relative to baseline—assessed on day 5, day 14, and day 21  
2. Number of participants hospitalized and/or requiring repeat ER visits  
3. ICU length of stay  
4. Number of days on a ventilator—if put on a ventilator | Treatment of COVID-19 in the outpatient setting                                  | Recruiting phase 4: Experimental Arm 1, hydroxychloroquine + azithromycin + zinc sulfate  
Experimental Arm 2, hydroxychloroquine + doxycycline + zinc sulfate |
| NCT04358081*     | Percentage of participants who achieve clinical response                          | Patients with moderate and severe COVID-19 disease                               | Recruiting phase 3: Drug: HCQ  
Drug: HCQ + AZT  
Drug: Placebo |
| NCT0435552*      | World Health Organization (WHO) ordinal scale measured at 14 days after enrolment | Severe SARS-CoV-2 infection                                                      | Recruiting phase 2: Active Comparator, standard of care; Experimental arm 1, standard of care plus hydroxychloroquine; Experimental arm 2, standard of care plus azithromycin; Experimental arm 3, standard of care plus hydroxychloroquine plus azithromycin |
| CTRI/2020/03/024402 | Time to clinical improvement                                                    | Moderate to high risk of exposure to infected patients during the study period  
Healthy at the time of enrolment without any symptoms suggestive of any viral infection | Recruiting phase 3: Randomized, Parallel Group, Active Controlled Trial |
| CTRI/2020/05/025067 | Proportion of laboratory confirmed symptomatic COVID-19 cases between the groups at the end of 6 months | All HCWs directly exposed to confirmed COVID-19 patients                          | Randomized, Parallel Group Trial  
Comparator arm: PPE; Interventional arm: HCQ |

*have recruited moderate and severe COVID-19 patients
Torsade de pointes (TdP) is a form of polymorphic ventricular tachycardia that occurs when the action potential duration of ventricular myocardial cells is prolonged. It is associated with long QT syndrome (LQTS), Brugada syndrome, and other genetic channelopathies. The development of prolonged QT is seen in the deaths across many countries [34], and probable Ethnic variations have come to focus after the discrepancies Asians and Arrhythmias

Ethnic variations have come to focus after the discrepancies seen in the deaths across many countries [34], and probable reasons for the minorities to suffer more from COVID-19 are increased admission risk for acute respiratory tract infections [35], increased vitamin D deficiency prevalence [36], country-specific vaccination policies [37], and increased inflammatory markers with high CV risk [38]. Studies have shown that Asians are different in many genetical aspects like the absence of the polymorphic enzyme, CYP2C19, in almost 20% of the population, which helps in the metabolism of proton pump inhibitors (e.g., pantoprazole, lansoprazole, omeprazole), antidepressants (e.g., amitriptyline, citalopram), and antineoplastic drugs (e.g., cyclophosphamide) [39]. Higher polymorphisms are seen in gene CYP2D6, which are higher in white Caucasians and, hence, are more predisposed to drug-induced prolonged QTc [40]. The frequency of variant KCNH2 alleles are much more in Caucasians and are much more predisposed to develop drug-induced prolonged QT [41]. Brugada syndrome, an SCN5A (cardiac sodium channel gene)-linked genetic channelopathy predisposing to sudden cardiac death, is nine times and 36 times more common in Asians than Caucasians and Hispanics, respectively [42, 43]. Atrial fibrillation (AF) seems to be lower in incidence in Asians than the Western population [44]. Hsu et al. found that individuals of Asian races commonly have the right anterior accessory pathways [46]. There is also variation in gene expressions related to the long QT syndrome (LQTS), where Asians show KCNQ1 G643S polymorphism in a higher degree than Caucasians [47]. Polymorphisms are often ethnicity specific like HERG P448R and A915V in Asians only [47]. Genes predisposing an individual to drug-induced torsade de pointes are HERG–P347S, R784W [48], SCN5A–L1825P, S1102Y [49], etc. A study combining both retrospective approach and prospective approach found 25% deaths in sudden cardiac deaths (SCD) category in their 5-year retrospective approach and 21 SCD victims in their 2-year prospective approach, out of which arrhythmogenic right ventricular cardiomyopathy constituted 10%, hypertrophic cardiomyopathy shared 5%, and 85% had negative autopsy [50]. A retrospective case-control study to determine the lower risk of AF in South Asians, involving 60 South Asians and 60 Caucasians, found that the left atrial size was smaller in South Asians as compared with Caucasians with lower left ventricular mass (p = 0.022), all of which might lead to a reduced risk of arrhythmogenic substrate formation (e.g., reentry circuit, fibrosis development) [51]. Another prospective study involving both Caucasians and South Asians found that the South Asians had significantly narrower QRS complex (p < 0.001 for males and p = 0.002 for females), shorter QTc interval (p = 0.038, females), lower P wave dispersion (p = 0.039 for males and p = 0.004 for females), and lower supraventricular ectopic activity (p = 0.024 for males, p = 0.004 for females) [52].

**Conclusion**

It is likely that the severe COVID-19 patients are aged, fragile, and hemodynamically unstable, with multiple existing comorbidities, and, hence they are prone to develop cardiac arrhythmias of all sorts. From the above facts, we can see that Asians are less susceptible than Caucasians in developing cardiac arrhythmias in general, but the scenario might not be...
applicable in the face of a cytokine storm that goes on in the severe COVID-19 patients. Hence, in these situations, we must maintain extreme cautiousness while prescribing these combination drugs, which can prolong the QT interval. Severe COVID-19 patients should be kept out of these potential arrhythmogenic drug combinations until we get the results from dedicated randomized clinical trials (RCTs). Until that time, we must use HCQ as a prophylactic drug in that population who have a normal baseline QTc or in patients with mild disease and not having any previous myocardial injury or CV risk factor and should be followed up closely with serial ECGs if needed to see any change after starting the drug. Similarly, AZ use should be restricted to mild COVID-19 infections only until further data is available in critically ill patients from RCTs.

Compliance with Ethical Standards

Ethical Declaration Not required since it is an analysis of existing literatures without any direct patient participation.

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