Journal of Genetics and Cell Biology
JGCB, 5(1): 315-321
www.scitcentral.com

ISSN: 2639-3360

Original Research Article: Open Access

Investigation of the Potential Side Effects of Hydroxychloroquine Used for the Treatment of Covid-19 Patients with Glucose-6-Phosphate Dehydrogenase Deficiency: A Systematic Review

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Received December 24, 2021; Revised January 18, 2022; Accepted January 21, 2022

ABSTRACT

Background: The aim of the study is to evaluate the results of hydroxychloroquine/chloroquine used for the treatment of COVID-19 infection in patients with G6PD deficiency.

Methods: For the research, PubMed, Cochrane, Elsevier, up to Date, and Google Scholar databases were searched with the keywords "glucose-6-phosphate dehydrogenase deficiency and hydroxychloroquine and COVID-19", yielding a total of 85 articles. Retrieved articles were reviewed, 10 case reports were found related to the subject, their data were synthesized and a systematic review was performed.

Results: The mean age of the participants was 53.3±15.783 years. The duration of hydroxychloroquine/chloroquine use was 1-10 days. The common characteristics of the participants were as follows: hemolysis, male gender, ethnic regions where G6PD deficiency is more common, and absence of a previous history of hemolytic anemia. Hemolysis developed in patients independently of the amount of hydroxychloroquine/chloroquine used.

Discussion: We are of the opinion that it would be beneficial to limit the use of hydroxychloroquine/chloroquine in patients infected with COVID-19, especially in those whose ethnic origins are African, Asian, Mediterranean coasts and who are male. However, there is a need for further retrospective and prospective studies including more data on the subject.

Keywords: G6PD deficiency, Covid-19, Hydroxychloroquine, Side effect

INTRODUCTION & OBJECTIVES

Hydroxychloroquine (HCQ) and chloroquine (CQ) are drugs that have been used for the treatment of malaria since the 1930s. Later, it has started to be used for the treatment of rheumatological diseases such as systemic lupus erythematosus, rheumatoid arthritis, and Sjogren's syndrome [1].

CQ and HCQ are among the drugs tested for COVID-19 infection, which has been known since December 2019, and started to be used because of their antiviral effects [2,3]. The Food and Drug Administration (FDA) also recommended the use of HCQ in COVID-19 infection in its statement dated 27.04.2020 [4]. Gautret [5] also recommended HCQ for the treatment of COVID-19 infection as a result of their study. However, the use of HCQ for COVID-19 infection, which has many side effects, is controversial. Chorin [6] do not recommend HCQ for the treatment of COVID-19 infection due to QT prolongation. HCQ is also not recommended by the new Covid-19 treatment guidelines of the Centers for Disease Control and Prevention (CDC) [7].

G6pd deficiency is an X-linked recessive disease that can progress with hemolytic anemia. The risk of hemolytic crisis that may occur with the use of HCQ should be considered, especially in regions where G6PD deficiency is common. Afra [4] reported that acute hemolysis was observed during the COVID-19 treatment of individuals with G6PD

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Citation: Aşık M & Aşık Z. (2022) Investigation of the Potential Side Effects of Hydroxychloroquine Used for the Treatment of Covid-19 Patients with Glucose-6-Phosphate Dehydrogenase Deficiency: A Systematic Review. J Genet Cell Biol, 5(1): 315-321.

deficiency [8]. A study testing HCQ for COVID-19 infection in mice with human type G6PD deficiency for 5 days concluded that HCQ did not cause hemolytic anemia [9]. Moreover, a retrospective study published in 2017 identified 11 G6PD deficient patients using HCQ for the treatment of rheumatology disease. Hemolysis was not detected in these patients despite an HCQ exposure of 58.33 years or more [10].

The rationale for our systematic review is to provide evidence of this controversial situation. The study aimed to evaluate the results of HCQ/CQ use in COVID-19 patients with G6DP deficiency.

METHODS

Primarily, all studies using HCQ or CQ for the treatment of COVID-19 in patients with G6PD deficiency were included in the systematic review. Incomplete manuscripts, manuscripts without sufficient data for synthesis; reviews, and subjective reviews were excluded from the systematic review.

The present study protocol was reviewed and approved by T.R. Ministry of Health (approval No: 2021-02-19T05_57_27).

The keywords "glucose-6-phosphate dehydrogenase deficiency and hydroxychloroquine and COVID-19" were searched from databases in all languages without adding any restriction codes. The reviewed databases included PubMed, Cochrane, Elsevier, UpToDate, and Google Scholar. At the end of the search, 85 articles were reached with the keywords. Of the articles, 16 were obtained from PubMed, 9 from Elsevier, and 60 from Google Scholar. All articles have been reviewed 3 times by the authors. The last search was made on 05.03.2021. Eighty-five articles reached by search were evaluated in terms of duplication and 17 articles were eliminated due to duplication. The remaining 68 articles were reviewed with their titles and abstracts. Among these 68 articles, no original research article examining the results of HCQ use in COVID-19 patients with G6PD deficiency was found. When the irrelevant articles, reviews, and editorial notes were eliminated, a total of 14 case reports were reached. Fourteen case reports were reviewed with their full texts, and 10 were deemed suitable for systematic review. All selected articles were in English.

Criteria for inclusion in the systematic review were,

1. Being an article determined by systematic screening,
2. Being an article evaluating the results of using HCQ or CQ in the treatment of COVID-19 in patients with G6PD deficiency,
3. Being a completed article,
4. The article has enough data to be calculated and synthesized
5. The article was a case report.

For the systematic review, age, gender, chronic diseases, first measured hemoglobin value, lowest hemoglobin value, G6PD value, duration of HCQ use, amount of HCQ, other drugs used for the treatment of COVID-19 were recorded. Conversions were made between units for computation and synthesis. In the statistical analysis, the IBM SPSS 22.0 version was used and p values less than 0.05 were considered statistically significant.

Mean, standard deviation, minimum and maximum were used for descriptive statistics. Pearson correlation analysis was used for statistical evaluation of numerical data.

RESULTS

The PRISMA protocol was used for the study. The PRISMA flow diagram of the studies included for systematic review is represented in **Figure 1** [11].

Brief summaries of the 10 cases included in the study were as follows:

Case 1

A 68-year-old male patient, Congolese. The patient has a history of DM type-2, hypertension, chronic renal insufficiency, and stroke. The patient presented to the clinic with COVID-19 symptoms and was hospitalized and treated. Amoxicillin/clavulanate, piperacillin/tazobactam, and HCQ were given for COVID-19. During the treatment, the patient's breathing was supported by mechanical ventilation.

A single dose of 600 mg HCQ was given to the patient on the 6th day of hospitalization. While the Hb level was 12 g/dL on the first day of hospitalization, Hb was measured as 6.5 g/dL on the sixth day of hospitalization. During this period, total and direct bilirubin and LDH values increased. On the 7th day of hospitalization, G6PD was measured as 2.5 U/g Hb and the patient was diagnosed with G6PD deficiency [12].

Case 2

65-year-old male patient from Cameroon. The patient had DM type-2, hypertension diagnoses. Hb was measured as 13.3 g/dl at the time of admission of the patient who had no previous history of hemolysis. The patient with positive COVID-19 PCR test was initiated on HCQ and azithromycin. On the 5th day of treatment, total bilirubin and LDH levels increased and HCQ was discontinued. The patient's Hb measured on the 5th day was 7.2 g/dl. G6PD activity was measured as 0.2 U/g. The patient developed acute renal failure after acute hemolysis [13].

Case 3

A 57-year-old Nigerian male patient. The patient had diagnoses of DM type-2, hypertension, hypercholesterolemia, GER, and glaucoma. He had no previous history of hemolysis. Hb was measured as 12.4 g/dl at the time of admission. The patient was given piperacillin/tazobactam, azithromycin, HCQ, and ceftriaxone for COVID-19. The

patient was initiated on HCQ on the second day of treatment and developed signs of hemolysis on the eighth day of treatment. Hb was 6.6g/dl, bilirubin was 35mmol/L, LDH was 1636 U/L. G6PD activity was measured as 2.8 U/gHb and G6PD deficiency was diagnosed. Due to hemolysis, 2 units of RCC were transfused to the patient [14].

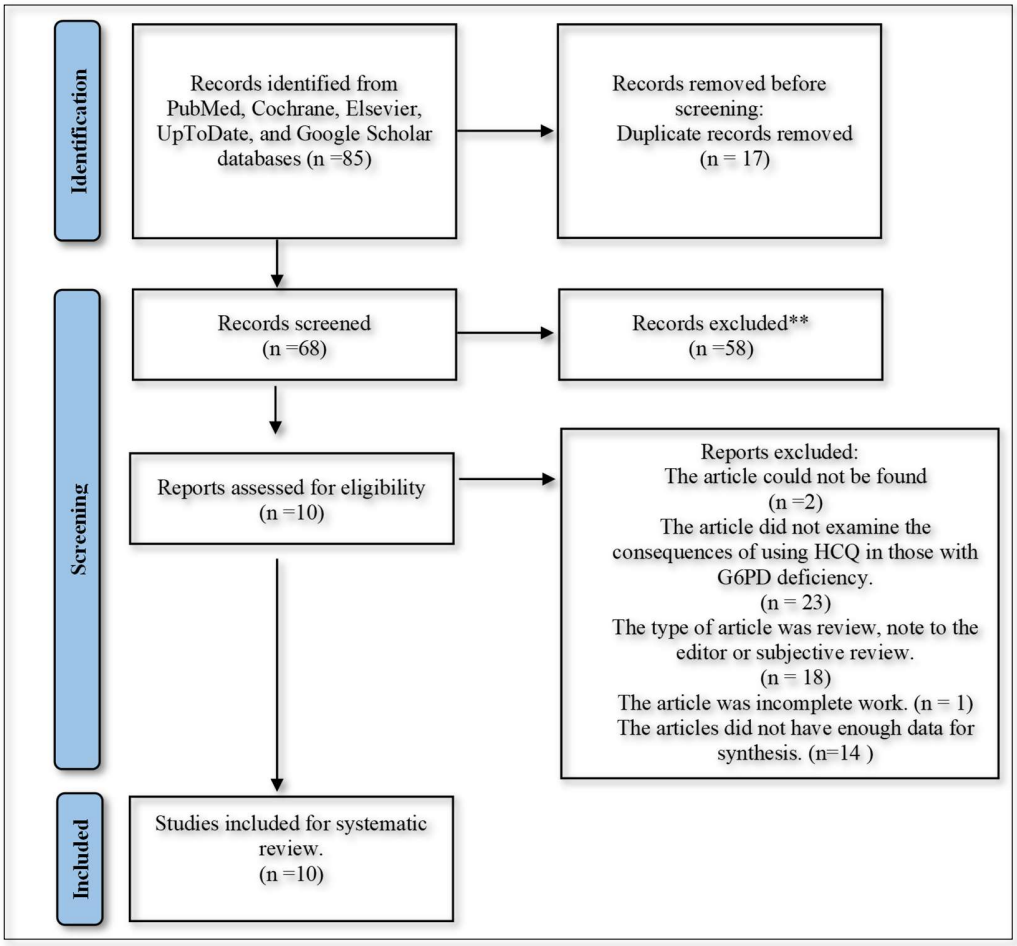

Figure 1. PRISMA flow diagram.

Case 4

A 26-year-old Pakistani male patient. He had no known comorbidity or history of hemolysis. The drugs given to the patient for COVID-19 were oseltamivir, lopinavir/ritonavir, azithromycin, HCQ, and ceftriaxone. The patient was scheduled to receive HCQ at a dose of 400 mg every 12 h, and a total of 3 doses of HCQ were given. G6PD level measured after the third dose was <9mU/10^9 RBCs. HCQ was discontinued after the patient was diagnosed with G6PD deficiency. The patient's Hb was 12.2 g/dL on the first day, 9.5 g/dL on the 12th day, and 11.6 g/dL on the 21st day [15].

- The patient's G6PD level was measured as <9mU/10^9 RBCs. In order to benefit from the data in systematic review, they were converted to U/gHb. The formula of U/gHb=[mU/10^9*1000]/[Hemoglobin(g/dL)*1000] was used for this [16]. According to the calculation, the patient's G6PD level was 0.094U/gHb.

Case 5

A 54-year-old male patient. Data on the ethnic origin of the patient reported from the USA could not be reached. The patient had uncomplicated DM. The patient was hospitalized for COVID-19. Azithromycin was started on the first day of hospitalization, and HCQ was started on the second day. Mechanical ventilation was started on the 4th day of hospitalization due to hypoxia. Subsequently, the patient with Coombs negative hemolysis was diagnosed with hemolytic anemia due to G6PD deficiency, and he died a short time later [17].

Case 6

A 72-year-old Italian male patient. He had no known neurological or hematological disease. The patient had a history of ischemic cardiomyopathy. The patient was given lopinavir, HCQ, and oxygen support for the treatment of COVID-19. The patient's first measured hemoglobin value

was 15 g/dL. The second hemoglobin measurement of the patient who developed hemolytic crisis 48 h after the start of the treatment was 12.5 g/dL. The patient was diagnosed with Mediterranean variant G6PD deficiency [18].

Case 7

A 32-year-old sub-Saharan African male patient. The patient's body mass index was 37.6 kg/m^2 and he had obesity. The patient was given HCQ twice a day for five days for COVID-19 infection. The patient's baseline hemoglobin was 10.0 g/dL and the hemoglobin on the 5th day of treatment was 7.7 g/dL. The evaluation showed no folate, B12, or iron deficiency. HIV and parvovirus B19 infection were negative. G6PD enzyme was detected as 0.2 U/g Hb and a diagnosis of G6PD deficiency was made [19].

Case 8

A 41-year-old male patient. He was African-Caribbean. The patient had type 2 DM. The patient was given 600 mg chloroquine on the first day, and 300mg chloroquine on the 2-5th days for the treatment of COVID-19. The patient's first measured hemoglobin level was 11.4 g/dL and 12 h after this measurement, the hemoglobin level was 8.9 g/dL. The patient exhibited signs of severe hemolysis. At the end of the investigation, the African variant G6PD deficiency was detected in the patient [20].

Case 9

A 64-year-old male patient. The patient was admitted from Qatar. He had known diseases of DM, hypothyroidism, and HT. The patient presented to the center with the symptoms of COVID-19. His admission hemoglobin was 13.2 g/dL. The patient was initiated on HCQ, azithromycin, ceftriaxone, oseltamivir, and lopinavir/ritonavir for the treatment of COVID-19. In addition, the patient continued to use his previous drugs including levothyroxine, losartan, and basal bolus insulin. During hospitalization, the hemoglobin value decreased to 11.3 g/dL, total bilirubin was 41µmol/L, direct bilirubin was 19.6 µmol/L, LDH was 252 U/L, and G6PD was 14 mU/10^9 RBCs. The patient was diagnosed with G6PD deficiency. HCQ treatment was completed to 10 days. During this period, the patient's hemoglobin levels decreased and increased again after the treatment was completed [21].

- The patient's G6PD level was 14 mU/10^9 RBC = 0.12 U/gHb [16].

Case 10

A 39-year-old African American male patient. The patient presented with weakness, acute renal failure, and liver damage.

Previously, the patient was given HCQ for COVID-19 pneumonia. The patient developed hemolysis, hemoglobin decreased from 12.2 g/dL to 6.3 g/dL, LDH was measured as 1758 U/L, and total bilirubin was measured as 25.4 mg/dL. Therefore, HCQ treatment was discontinued. The patient with increased methemoglobin level was diagnosed with G6PD deficiency. The patient received multiple RBC transfusions. However, the patient's severe hemolysis lasted for 10 days [22].

Some features of the articles included in the study and the cases examined are presented in **Table 1**.

Table 1. Features of the article.

Features of the Article		Characteristics of the Case						
First Author of the Article	Received Date	Age	Baseline Hb (g/dl)	Lowest Hb Measured (g/dl)	Amount of Hb Reduction (g/dL)	G6PD Value (U/gHb)	Duration of HCQ use (days)	Total HCQ received (mg)
Beauverd	15.04.2020	68	12	6.5	5.5	2.5	1	600
Maillart	28.04.2020	65	13.3	7.2	6.1	0.2	5	1200
Chaney	16.09.2020	57	12.4	6.6	5.8	2.8	-	-
Sasi	8.05.2020	26	12.2	9.5	2.7	0,09	2	1000
Naymagon	7.05.2020	54	-	-	-	-	-	-
Franceschi	20.03.2020	72	15	12.5	2.5	-	2	-
Mastroianni	7.06.2020	32	10	7.7	2.3	0.2	5	2400
Kuipers	10.05.2020	56	11.4	8.9	2.5		5	3000
Obeidat	11.07.2020	64	13.2	8.8	4.4	0.12	10	4000
Bhatia	18.10.2020	39	12.2	6.3	5.9	-	1	-

Nine cases included in the study included patients who used HCQ for COVID-19, and one patient used CQ. All patients were male. No patient had a known prior history of hemolysis and none were known to have prior G6PD deficiency. The ages of the patients ranged from 26 to 72 years, with a mean age of 53.300±15.783 years. The mean of the participants' first measured hemoglobin values was 12.411±1.378, and the mean of the lowest hemoglobin values measured was 8.222±1.979. The mean G6PD was 0.985±1.293.

Of the participants, 60% had DM and 40% had HT. Other than HCQ/CQ, azithromycin was used in 50%, ceftriaxone in 30%, oseltamivir in 20%, lopinavir/ritonavir in 30%, piperacillin/tazobactam in 20%, and amoxicillin/clavulanate in 10% of the patients for COVID-19 treatment.

When we examined the rate of change in the hemoglobin value of the participants in the study, the hemoglobin values of 9 of them were reached. The difference between the initial and lowest measured hemoglobin values ranged between 6.10 and 2.30 g/dL.

There was a positive correlation between the decrease in hemoglobin values of the participants and their G6PD levels (P=0.236 and r=0.572).

There was a positive correlation between age and the participants' baseline hemoglobin value (P=0.642 and r=0.642).

There was a positive correlation between age and the lowest hemoglobin value measured (P=0.638 and r=0.182).

There was a positive correlation between age and the decrease in hemoglobin value (P=0.413 and r=0.312).

There was a negative correlation between the total amount of HCQ used by the participants and the change in hemoglobin (P=0.494 and r=-0.352).

Furthermore, there was a negative correlation between the duration of HCQ use and the change in hemoglobin (P=0.826 and r=0.093).

DISCUSSION

All of the patients we examined in the study were patients who received different treatments in different countries for their COVID-19 symptoms. However, all patients used antimalarial and/or antirheumatic CQ/HCQ for the treatment of COVID-19, and all patients developed hemolysis. It is known that hemolysis may develop with the use of HCQ in patients with G6PD deficiency. There are many studies on the subject in the literature [23,24]. This was consistent with our results.

None of the patients we examined in the study were known to have G6PD deficiency previously and none of them had a previous history of hemolysis. For this reason, patients were not evaluated for G6PD deficiency when COVID-19 treatments were adjusted. Eight of the patients included in the study were of African ethnicity, while one was Italian. All these countries were countries where G6PD deficiency was seen more intensely. According to the World Health Organization, the regions where G6PD deficiency is most commonly seen in men are Africa, Asia, and America in order of frequency [25]. This is consistent with our results. This result reminds us of the importance of evaluating ethnic background in people with signs of acute hemolysis, whether or not they have a previous history of hemolysis.

Similarly, to our study, Onori and colleagues also investigated the relationship between HCQ and G6PD deciency in their research [26]. In this study, all patients are male, no patient knows that they have G6PD deficiency before, and all of them had hemolysis within the first week of drug use. The results support our research.

As is known, the FDA recommended the use of HCQ in April 2020. The use of HCQ was cancelled on June 2020 [4,27]. In 9 October 2020, the use of HCQ for the treatment of COVID-19 infection was removed from the guidelines of CDC. It is not included in the new COVID-19 treatment guideline [7]. The data collection process of our study was terminated in March 2021. However, the last article included in the study was accepted in October 2020. In the 6-month period from October 2020 to March 2021, no cases of hemolysis due to HCQ use were reported in COVID-19 patients with G6PD deficiency. This can be explained by the fact that countries one by one stopped using HCQ for the treatment of COVID-19 infection.

In our study, a positive correlation was found between the G6PD values and hemoglobin levels of the patients. This result is parallel with the clinical reflection of G6PD deficiency [28].

In the study, the amount of decrease in hemoglobin level increased as the age of the participants increased. In other words, even if the first measured hemoglobin level was higher in older patients, we can say that more severe hemolysis developed. In the literature, there was no study evaluating the causes of hemolysis severity in G6PD deficiency in adults. However, a study reported that hemolysis may be more severe in children with G6PD deficiency in the presence of young age, male gender, and negative family history [11]. There is a need for extensive studies on the subject in adult individuals.

In the study, a negative correlation was unexpectedly found between the duration of HCQ use and the amount of hemoglobin reduction in patients with higher HCQ levels. The results were not statistically significant. It should be kept in mind that patients with G6PD deficiency may develop hemolysis regardless of the duration and amount of HCQ use, even with the use of very small amounts of HCQ.

CONCLUSIONS

Different treatment protocols have been used for the treatment of COVID-19 disease since December 2019, when the disease

was first reported. While some of these drugs are still used such as dexamethasone, the use of some drugs has been stopped. The long-term course of the disease, its complications, and the long-term effects of the drugs used are unknown. Perhaps, the currently used treatment protocols may not be used over time, or dose changes may be made in drugs. In our systematic review, 10 patients with G6PD deficiency treated with HCQ/CQ for COVID-19 infection were examined. The common characteristics of the participants were as follows: hemolysis, male gender, ethnic regions where G6PD deficiency is more common, and absence of a previous history of hemolytic anemia. Hemolysis developed in patients independently of the amount of HCQ/CQ used. We think that it would be beneficial to limit the use of HCQ/CQ in patients infected with COVID-19, especially in those with ethnic origins of Africa, Asia, Mediterranean coasts, with male gender. However, there is a need for further retrospective and prospective studies including more data on the subject.

DISCLOSURE

The authors have no conflict of interest.

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