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Before Saying Farewell to Hydroxychloroquine Usage in Practice: Evaluation of Our Safety Data on Hydroxychloroquine Treatment in Children with COVID-19

Uygulamada Hidroksiklorokin Kullanımına Veda Öncesi: COVID-19'lu Çocuklarda Hidroksiklorokin Tedavisine İlişkin Güvenlik Verilerimizin Değerlendirilmesi

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Abstract

Objective: This study aimed to evaluate the adverse effects of hydroxychloroquine (HCQ) in children with COVID-19.

Material and Methods: This study was conducted between March-August 2020 at a referral tertiary hospital for pediatric infectious diseases in the Aegean Region of Turkey. All hospitalized children with COVID-19 who were received HCQ include in this study. An electrocardiogram (ECG) was performed prior to the initiation of HCQ and at certain times (first and 24th hours of HCQ administration and two hours after the final dose of HCQ) during treatment. Adverse effects associated with HCQ were evaluated during the hospitalization and also the first and second months after discharge.

Results: A total of 62 children with COVID-19 who administered HCQ treatment were evaluated. Of these, 35 (56.5%) were girls and 27 (43.5%) were boys. The mean age 13.7 ± 3.0 years (range 6.0 to 18.0 years). Prior to the admission, none of the patients had arrhythmia, cardiovascular disease, or any cardiotoxic drugs usage. There was no abnormality on the baseline and following ECGs during the treatment with HCQ. Thirteen patients had nausea (20.9%) and 10 patients (17.7%) had mild abdominal pain. None of the patients had no arrhythmia.

Conclusion: No cardiac side effects were observed in our patients. However, it is not possible to give a general statement on the safety data of HCQ therapy without any randomized controlled large-scale studies.

Keywords: Coronavirus disease 2019 (COVID-19), hydroxychloroquine (HCQ), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

Öz

Giriş: Bu çalışmada, COVID-19'lu çocuklarda hidroksiklorokin (HCQ) kullanımının yan etkilerinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Bu çalışma, Mart-Ağustos 2020 tarihleri arasında Türkiye'nin Ege bölgesinde bulunan çocuk enfeksiyon hastalıkları için üçüncü basamak bir referans hastanede yapılmıştır. Çalışmaya COVID-19 tanısıyla hastanede yatan ve hidroksiklorokin tedavisi verilen tüm çocuklar dahil edildi. Hastalara hidroksiklorokin tedavisi başlamadan önce ve tedavi sırasında belirlenen zamanlarda (hidroksiklorokin başlanmasının ardından birinci saatte, 24. saatte ve son hidroksiklorokin dozundan iki saat sonra) elektrokardiyogram (EKG) çekildi. Hastalar hastanede yattıkları sürece ve taburcu olduktan sonra birinci ve ikinci ayda hidroksiklorokin ile ilişkili yan etkiler açısından değerlendirildi.

Bulgular: Hidroksiklorokin tedavisi alan COVID-19'lu 62 çocuk değerlendirildi. Bunların 35 (%56.5)'i kız, 27 (%43.5)'si erkekti. Ortalama yaş 13.7 ± 3.0 yıl (6.0-18.0 yıl) bulundu. Hastaneye yatmadan önce, hastaların hiçbirinde aritmi, kardiyovasküler hastalık veya herhangi bir kardiyotoksik ilaç kullanımı öyküsü yoktu. Hastaların hidroksiklorokin tedavisine başlamadan önce ve tedavi sırasında çekilen takip EKG'lerinde herhangi bir anormallik saptanmadı. On üç hastada (%20.9) bulantı, 10 hastada (%17.7) hafif karın ağrısı oldu. Hastaların hiçbirinde aritmi gözlenmedi.

Sonuç: Hastalarımızda herhangi bir kardiyak yan etki gözlenmedi. Ancak, büyük ölçekli randomize kontrollü çalışmalar olmadan HCQ tedavisinin güvenliği ile ilgili öneride bulunmak mümkün değildir.

Anahtar Kelimeler: Koronavirüs hastalığı 2019 (COVID-19), hidroksiklorokin (HCQ), ağır akut solunum yetmezliği sendromu koronavirüs 2 (SARS-CoV-2)

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Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, defined as coronavirus disease 2019 (COVID-19), was identified as the cause of numerous viral pneumonia cases in Wuhan, in December 2019 (1). World Health Organization (WHO), on March 11, declared COVID-19 a pandemic (2).

At the beginning of the COVID-19 pandemic, to determine the most effective treatment strategy, several drugs were investigated as a specific treatment option such as lopinavir-ritonavir, hydroxychloroquine (HCQ), remdesivir, azithromycin, oseltamivir, favipravir, or ribavirin (3). Chloroquine, a widely-used anti-malarial, and autoimmune disease drug have firstly been reported as a potential antiviral drug against the SARS-CoV-2 in China (4). Wang et al. revealed that chloroquine functioned at the entrances, and at post entry stages of the virus, consequently it was found highly effective in the control of virus in vitro (4).

Beside its cost effectiveness and easily accessibility, HCQ has a safety profile that is well known in the treatment of non-COVID-19 diseases, especially for malaria. On the other hand, its potentially adverse effects associated with the higher doses used for prolonged periods must be kept in mind. Gastrointestinal symptoms, pruritus, and dermatological changes are more common side effects. Rare but severe side effects of HCQ include myopathy of proximal muscles, cardiotoxicity (prolonged Q-T, arrhythmia), and irreversible retinopathy (5).

There is limited evidence concerning about the adverse effects and also the efficacy of HCQ in COVID-19 especially in children. In the center where this study was conducted, all patients were treated according to the national guidelines of the Ministry of Health. This retrospective cohort study focused on the side effects of HCQ use in the treatment of COVID-19 in children.

Materials and Methods

This study was conducted between March 2020-August 2020 at University of Health Sciences Dr. Behçet Uz Child Disease and Pediatric Surgery Training and Research Hospital, a tertiary referral hospital for pediatric infectious diseases in the Aegean Region of Turkey. Data of the patients was collected from medical records retrospectively including information on demographic characteristics (age, gender, underlying diseases); length of hospital stay (LOS); dosage, duration, and outcome of HCQ therapy.

In the study center, all patients older than six years old were treated properly to the national guidelines of the Ministry of Health including diagnosis and treatment strategies. According to the recommendations of the national guidelines and also the advices of the authorities worldwide, at the beginning of the pandemic through August, 2020, HCQ sulfate, was administered orally at a dosage of 6.5 mg/kg/dose twice daily on the first day (maximum dose on the first day was 400 mg/dose); then 3.25 mg/kg/dose twice daily on days two through five (maximum dose on days two through five was 200 mg/dose) (6). According to the protocol of the hospital, serum glucose-six-phosphate dehydrogenase (G6PD) deficiency was screened (7). Electrocardiogram (ECG) was performed in all patients prior to the initiation of HCQ, and during the follow-up, control ECGs were monitored at the 1st and 24th hours of the HCQ therapy. The final ECG was performed two hours after the final dose of HCQ. Patients were evaluated in terms of HCQ common side effects such as skin rash, itching, abdominal pain, diarrhea, anorexia, headache, tinnitus, dizziness, and blurred vision. Hydroxychloroquine was not administered in the patients younger than six years of age who were not candidates for HCQ, and lacking the cognitive capacity to answer questions about vision. The retinal evaluation of patients was not routinely performed. The flow algorithm was illustrated in Figure 1.

All patients' caregivers were called and questioned twice about the health status of individuals by phone in the first and second months after discharge.

Table 1. General characteristics of the patients and side effects associated to the use of hydroxychloroquine

Gender	n (%)
Female	35 (56.5)
Male	27 (43.5)
Age (mean)	13.7 ± 3.0 years (6-18 years)
	n (%)
Underlying disease	10 (16.1)
Asthma	5 (8.1)
Cerebral palsy	2 (3.2)
Familial Mediterranean Fever,	1 (1.6)
Idiopathic thrombocytopenic purpura,	1 (1.6)
Immunodeficiency	1 (1.6)
Length of stay in hospital (mean)	6.5 ± 3.8 days (5-28 days)
Side effects	n (%)
Nause	13 (20.9)
Abdominal pain	10 (17.7)
Diarrhea	Not observed
Skin rash or itching	Not observed
Visual problems	Not observed
Tinnitus	Not observed
Arrhythmia	Not observed

Results

During the study period, a total of 62 children with COVID-19 who received HCQ treatment were evaluated. The mean age 13.7 ± 3.0 years (range 6.0 to 18.0 years). Thirty-five (56.5%)

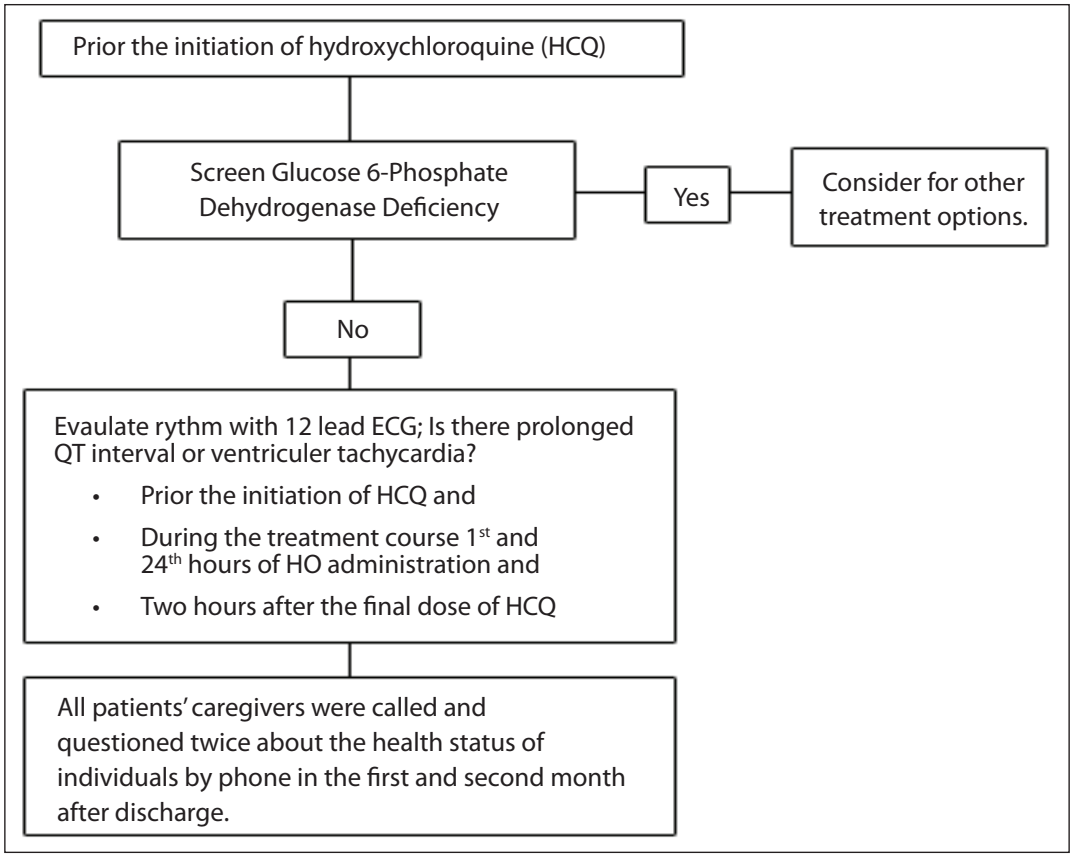

Figure 1. Flow diagram.

patients were female and 27 (43.5%) were male. Among patients, 10 (16.1%) had underlying disease including bronchial asthma in five patients, cerebral palsy in two patients, and one each with familial Mediterranean fever, idiopathic thrombocytopenic purpura, and immunodeficiency. The mean LOS was 6.5 ± 3.8 days (range to 5.0 to 28.0 days). Serum G6PD levels of all patients were within normal limits.

None of the patients had arrhythmia, cardiovascular disease, or any cardiotoxic drug usage in the study group prior to the admission. There was no abnormality on the baseline ECG and the following ECGs during the treatment. The QTc interval in the ECGs of the patients was within the normal range for their age. QTc prolongation was not observed in any of the patients before and after HCQ treatment. In regards to other adverse effects among the patients, 13 patients had nausea (20.9%) and 10 patients (17.7%) had mild abdominal pain. None of these complaints were severe to require interruption or stop the HCQ therapy. No skin rash was observed and no visual problem was observed among the patients.

Two patients' caregivers could not be contacted by phone after discharge. According to the statements of remaining 60 caregivers on phone, there was no mortality or complaints among the patients associated with HCQ during the long time period.

Discussion

This retrospective study includes one of the largest pediatric populations who received HCQ therapy, emphasized that there was no serious adverse effect associated with HCQ treatment in the children with COVID-19. Detected adverse effects were closely related to gastrointestinal system which had no necessity for discontinuing the therapy.

A retrospective, observational study reported that receiving hydroxychloroquine reduces mortality in COVID-19 (8). Results from the Solidarity Therapeutics Trial, coordinated by WHO, indicated that HCQ had little or no effect on overall mortality, initiation of ventilation, and length of hospital stay in hospitalized COVID-19. In other respects, it must be mentioned that the large multicenter randomized controlled trial revealed HCQ use was not associated with serious adverse effects (9). As a result of a meta-analysis, there was no progress of clinical courses such as a significant decline in mortality with HCQ use, but a higher risk of ECG abnormalities and arrhythmia was associated with HCQ therapy (10). Another meta-analysis stated the overall mortality as 2.5 times greater among the group treated with HCQ (11).

The recommendations of health authorities about HCQ therapy on COVID-19 differed based on data of literature during the pandemic. In March 2020, the United States Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) allowing HCQ to be administered in COVID-19 patients. However, FDA annulled the EUA by the reason of potential benefits of HCQ may not predominate its potential risks, as of June 15, 2020 (12,13). As for our own national guide recommendations: Although, HCQ was among the treatment options in the national guidelines of the Turkish Ministry of Health until May 2021, the guideline was updated on May 20, 2021, and currently, HCQ removed from the treatment options (7,14).

There is no reliable data on the effect of HCQ in children with COVID-19. Although the above-indicated meta-analysis results mentioned increase side effects associated with HCQ therapy (10,11), opposite the findings, any side effects related to cardiac system involvement were not experienced and none of the patients had mortality or morbidity associated with COVID-19 in the current study population. In addition, none of the patients had adverse effects during the follow after discharge. Nevertheless, because of its retrospective design and lack of randomization, the efficacy of HCQ could not be investigated in the current study. The patient groups of the studies examined in these meta-analyzes are predominantly adults. Some conditions such as underlying chronic cardiac diseases, use of drugs that cardiotoxic or have a predisposing effect on arrhythmias are more common among adults than children. This may have enhanced the potential risks of HCQ usage. In a recent multicenter study, HCQ was administered to 78 SARS-CoV-2 PCR positive children in Turkey. As reported by this study, no ECG abnormalities were observed as a result of the HCQ adverse effect (15). These findings are consistent with our outcomes. Thus, we speculated that HCQ may be safety and beneficial in the treatment of COVID-19 in children.

There are several limitations in this study. Firstly, this was a retrospective study, which has innate restrictions when compared to randomized clinical trials. Secondly, the study was including one single center's patients. Thirdly, this study focused only on the adverse effect of HCQ, but its efficacy was not evaluated. However, it must be emphasized that the study includes one of the largest pediatric population treated with HCQ for COVID-19. The other valuable characteristic is that studies evaluating the use of HCQ in children are extremely rare in the literature.

Conclusion

In conclusion, in the present study, mild and transient adverse effects such as abdominal pain and nausea were detected in 20.9% of the patients during HCQ therapy. In this study, we observed no cardiac side effects in our patients. However, due to the limitations mentioned above, it is not possible to give a general statement on safety data of HCQ therapy without any randomized controlled large scale studies.

Ethics Committe Approval: Ethical approval was received for this research from University of Health Sciences Dr. Behçet Uz Child Disease and Pediatric Surgery Training and Research Hospital Ethics Committee (Approval number: 546-2021/08-06, Date: 22.04.2021).

Informed Consent: Patient consent was obtained.

Peer-review: Externally peer-reviewed.

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