Original Study

Slight High-Frequency Hearing Loss, Effect of COVID-19 or Hydroxychloroquine Usage?

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Background and Objectives: Concerns about ototoxic and vestibulotoxic effects have been raised with the use of antiviruses in the treatment of COVID-19. This study aimed to determine the effect of hydroxychloroquine (HCQ) and examine the auditory system and its associated auditory and vestibular symptoms in patients with COVID-19.
Study Design: Prospective study.
Patients: Thirty patients with a history of HCQ (HCQ+) and 30 patients without drug use (HCQ−), and 30 healthy adults as the control group participated.
Main Outcome Measure(s): Audiological assessments and evaluation of audio-vestibular symptoms. Evaluations were also repeated 1 month later.
Results: Both HCQ+ and HCQ− groups showed poor pure-tone audiometry (PTA) thresholds and decreased transient evoked otoacoustic emission amplitudes at high frequencies in comparison to the healthy group. Despite the lack of significant differences in PTA between the two groups of patients, the differences in transient evoked otoacoustic emission amplitudes were significant. PTA thresholds and otoacoustic emission showed improvement after 1 month. Dizziness was the most common symptom that was reduced after 1 month.
Conclusion: Slight hearing loss was seen in patients with COVID-19 with or without HCQ. Also, hearing thresholds in the HCQ+ group did not show a significant difference compared with the HCQ− group. Nevertheless, it seems that more damage is done to the hair cells of patients with HCQ intake than in other patients. Hence, the ototoxicity effect of high doses of HCQ use in the COVID-19 patients should be considered. A relative improvement in the hearing was seen over time in both patient groups.
Key Words: COVID-19—Hearing loss—Hydroxychloroquine—Ototoxicity.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) was declared a pandemic by the World Health Organization (WHO) on March 11, 2020, and became one of the greatest challenges of the century, despite the growth of technology and health knowledge (1). The disease first presented as a respiratory illness caused by severe acute respiratory syndrome coronavirus. Then, it revealed other short-term or long-term symptoms. In the past 2 years, several case reports and case series reported that COVID-19 also caused inflammation, which might contribute to a sensorineural hearing loss (1,2). According to a meta-analysis, the pooled estimate of the prevalence of hearing loss, tinnitus, and rotatory vertigo was 7.6% (95% confidence interval [CI], 2.5–15.1%), 14.8% (95% CI, 6.3–26.1%), and 7.2% (95% CI, 0.01–26.4%) using the retrospective recall method, respectively (1). Most studies on the effect of COVID-19 on the auditory and vestibular system have been done using a questionnaire and only carried out psychometric assessments (3), and only a few cross-sectional studies performed a diagnostic audiological evaluation to determine the presence of hearing loss (4–6). The first cross-sectional study in this area was conducted by Mustafa (6), who reported poor hearing thresholds at high frequencies. Lower amplitudes of otoacoustic emission (OAE) were also observed, consistent with a study by Daikhes et al. (4). However, Dror et al. (5) found no significant differences in distortion product otoacoustic emission, transient evoked otoacoustic emission (TEOAE), or auditory brainstem responses between asymptomatic severe acute respiratory syndrome coronavirus patients and the control group. These researches raised concerns about the effect of ototoxic drugs, which were widely used during the COVID-19 pandemic, and the effect of comorbidities (1,6). Ototoxicity refers to the toxic capacity of medications that can be harmful to cochlear, vestibular, and auditory nerve cells and is generally associated with symptoms such as sensorineural hearing loss, tinnitus, and imbalance (7). Among the wide range of drugs used to treat COVID-19, hydroxychloroquine (HCQ)

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is considered a drug that may be ototoxic (8). The WHO guideline does not strongly recommend using this drug with any severity of the disease or symptoms because of the increased risk of cardiotoxicity (9). However, during the COVID-19 period, numerous patients have used HCQ, especially at the beginning of a pandemic (8–10). Although a recent study showed hair cell damage after exposure to chloroquine (CQ)/HCQ in zebrafish lateral line and neonatal mouse cochlear cultures, this drop was significantly dose dependent (11). In the human domain, most of the studies that reported the ototoxic effects of HCQ on the auditory system and balance in treating other diseases were case reports and were prescribed at different doses and durations (8,10). Sensorineural hearing loss and tinnitus after CQ or HCQ administration for other diseases can be temporary; however, there are also reports of persistent auditory and vestibular dysfunction (8,10,12,13). However, the question is whether the dose and duration of HCQ in the treatment of COVID-19 could have devastating effects on the auditory and balance system. Because no study has compared audiological assessments in patients with COVID-19 with and without HCQ, auditory system function between patients with and without HCQ and the control group was compared in this study. Also, reversible or irreversible results were assessed by repeating the evaluations 1 month after the initial tests.

METHODS

Selection and Description of Participants

This prospective study enrolled individuals who tested positive for COVID-19 infection by reverse transcription–polymerase chain reaction. These participants were selected among employees who contracted COVID-19 during the pandemic and were required to see a physician 15 days after receiving a positive polymerase chain reaction test result to receive a health card allowing them to return to work. The inclusion criteria included being between the ages of 20 and 48 years to minimize the natural effects of aging-related hearing loss; having no history of hearing loss or any condition that could result in hearing loss, tinnitus, vertigo, or balance problems; and not having a history of accidents, head injury, noise exposure, or use of ototoxic drugs, and also having no underlying diseases such as diabetes, heart disease, or kidney disease as comorbidities. This information was extracted from patients' records because they were examined at this center on a regular basis for medical examinations and hearing tests. As a result, samples were taken from individuals whose previous hearing assessment indicated a hearing threshold of 0- to 15-dB hearing level. Another entrance criterion was a history of HCQ use during COVID-19. As a consequence, our patients were separated into 30 patients with a history of HCQ intake and 30 patients without a history of HCQ consumption. The protocol used to treat COVID-19 in the patients who participated in this study was similar, except for the use or nonuse of HCQ. Failure to use another ototoxic drug to treat COVID-19 was another entry condition. In addition, HCQ was used exclusively to treat COVID-19 disease, and none of the patients had previously received HCQ for an autoimmune disorder such as rheumatoid arthritis. The inclusion criteria for the 30 healthy subjects in the control group were similar to those for the patient groups, with the exception of a history of COVID-19 disease.

In WHO guidelines, HCQ prescription value was 800 mg once at the first dose, then 200 mg twice daily for 4 to 7 days in the mild clinical form of disease without optional additional medicine (14). Also, According to Diagnostic Therapeutic Flowchart for COVID-19 update (December 2 2020), HCQ/CQ is recommended only in patients who do not indicate hospitalization, specifically in the first week of onset of symptoms in our country. Hence, HCQ sulfate 200 mg was administered as two tablets twice daily on the first day, followed by one tablet twice daily for 7 to 14 days (15).

Procedure

This study was conducted in two phases at two times (precisely at the end of the second immediately after a definitive diagnosis of COVID-19 disease in the patient group and 1 month after the first phase).

In the study's first phase, an accurate history was taken to determine all participants' admission and otology examination conditions, including otoscopy. Then, the patients were asked to complete a checklist designed to assess the prevalence of symptoms related to the audiovestibular system after COVID-19 infection in both patient groups treated with and without HCQ. These symptoms must have appeared after COVID-19. The checklist was designed in a similar way to the study questionnaire of Korkmaz et al. (16). This checklist had two sections: demographic data and health status and information about the prevalence of audiovestibular symptoms, which was gathered through an interview. Air- and bone-conduction thresholds were evaluated using the modified Hughson–Westlake method with the Midimate Interacoustic Audiometer (Interacoustic Co., Assens, Denmark) equipped with TDH39 headphones and BV71 bone vibrator at 250, 500, 1,000, 2,000, 4,000, 6,000, and 8,000 Hz (17). Immittance audiometry was performed to confirm the normal condition of the middle ear with tympanogram type A. The signal-to-noise ratio (SNR) of TEOAE, which indicates the function of the inner ear, especially OHCs, and is used as a method for ototoxicity monitoring (18), was recorded in all participants in both groups at 1,000, 2,000, 3,000, 4,000, and 5,000 Hz using the ECOLAB (Labat Co., mestre (venezia), Italy). The stimuli consisted of a nonlinear click delivered at about 80-dB peak sound pressure level in the ear canal. The responses were recorded by presenting 1,000 stimuli within permissible noise limits without rejection. This study considered the acceptable repeatability percentage greater than 70% (19). All tests were performed in a double-walled, sound-treated booth within permissible noise limits (<30 dB) (17). The second stage was performed exactly 1 month after the first phase evaluations; all tests and checklists were repeated to monitor the persistence of the findings in COVID-19 patients. Therefore, audiovestibular symptoms that persisted or appeared recently were reported. In the first phase and the second phase, all tests were performed on both the patient and control groups.

Written informed consent was obtained from all participants. The Ethics Committee approved this study by the University of Medical Sciences (IR.TUMS.FNM.REC.1399.2.214).

Statistical Analysis

Data analysis was done using the SPSS software version 22 (SPSS Inc., Chicago, IL). Quantitative variables are presented as mean ± standard deviation (SD), and qualitative variables are expressed as percentages. One-way analysis of variance was used to compare groups, and then the Bonferroni post hoc test was used for pairwise comparisons, a more stringent criterion for statistical significance. Paired *t* test was used to compare results between the first and second phases of the study in the patient with and without HCQ administration and the control group. All *p* values were two-sided, and the statistical significance was set at $p < 0.05$, with a 95% CI.

RESULTS

Demographic Characteristics

Thirty patients with HCQ consumption with a mean ± SD age of 33.36 ± 7.07 years (range, 23–48 yr) and 30 patients without HCQ consumption with a mean ± SD age of 31.96 ± 8.17 years (range, 20–48 yr) participated in this study. Twenty-four patients (80%) had a history of HCQ use for 5 days, four patients had a history of HCQ use for 4 days, and two patients had a history of HCQ use for 6 days. The control group also included 30 participants with a mean ± SD age of 32.26 ± 7.81 years. There was no significant difference in age ($F_{2,117} = 0.28$, $p = 0.75$) between the three groups. Also, 21 participants (81%) were male in each group. All patients participating in the first phase also participated in the second phase.

Pure-Tone Audiometry Thresholds

As seen in Table 1, the results of statistical analysis using one-way analysis of variance test showed a significant difference between patients treated with and without HCQ groups and the control group at 2 to 8 kHz ($p < 0.001$). Post hoc analysis showed that patients treated with and without HCQ have a higher mean of pure-tone audiometry (PTA) thresholds compared with the control group at the high frequencies ($p < 0.001$). However, there was no significant difference in the results of the PTA threshold at all frequencies between patients treated with and without HCQ ($p > 0.05$).

First Phase Versus the Second Phase

A comparison of the mean of PTA thresholds between the first phase and the second phase in patients treated without HCQ using the pair *t* test is shown in Figure 1. The results showed a significant difference at 1 kHz ($t_{59} = 2.16$, $p < 0.05$), 2 kHz ($t_{59} = 2.68$), 4 kHz ($t_{59} = 3.93$), 6 kHz ($t_{59} = 3.76$), and 8 kHz ($t_{59} = 4.47$, $p < 0.001$ in all of them). Also, the mean of PTA thresholds after 1 month in patients treated with HCQ reduce significantly at 1 kHz ($t_{59} = 2.05$, $p < 0.05$), 2 kHz ($t_{59} = 2.87$), 4 kHz ($t_{59} = 3.29$, 6 kHz ($t_{59} = 2.45$), and 8 kHz ($t_{59} = 4.20$, $p < 0.01$ in all of them). Also, the comparison between the PTA thresholds of the control group in the two phases 1 and 2 did not show a significant difference in all frequencies ($p > 0.1$ in all of them).

SNRs in TEOAE

As shown in Table 2, the SNRs of the TEOAE test were significantly different between COVID-19 patients with and without a history of HCQ intake and the control group at the frequencies of 1 to 5 kHz (all $p < 0.001$). The post hoc comparison analysis results showed that the SNRs were significantly lower in both groups of patients than in the control group at all frequencies ($p < 0.001$). Also, there was a significant difference between both patient groups' SNRs at 2- to 5-kHz frequencies ($p \leq 0.05$).

First Phase Versus the Second Phase

Paired *t* test analysis showed a significant difference in the mean SNRs between the first and second phases in patients treated without HCQ at 2 kHz ($t_{59} = -2.20$, $p < 0.05$), 3 kHz ($t_{59} = -2.72$), 4 kHz ($t_{59} = -5.64$), and 5 kHz ($t_{59} = -6.27$, $p < 0.001$ in all of them). Also, the difference between the two phases in patients treated with HCQ was significant at 2 kHz ($t_{59} = -3.28$), 3 kHz ($t_{59} = -4.63$), 4 kHz ($t_{59} = -6.96$), and 5 kHz ($t_{59} = -10.12$, $p < 0.001$ in all of them; Fig. 2). Also, the comparison between the

TABLE 1. *Comparison of pure-tone audiometry thresholds at 0.25- to 8-kHz frequencies between patients with and without a history of hydroxychloroquine intake and the control group (n = 60 ears in each group)*

Frequency	Groups	Mean ± SD	*F*	*p*	Effect Size	Between Groups	MD	*p*
0.25	HCQ+	10.83 ± 1.87	0.32	0.91	—	C* HCQ+	−0.25	0.98
	HCQ−	10.67 ± 1.71				C* HCQ−	0.69	0.69
	C	10.58 ± 1.61				HCQ+* HCQ−	0.67	0.75
0.5	HCQ+	10.33 ± 1.25	1.46	0.24	—	C* HCQ+	−0.33	0.22
	HCQ−	10.08 ± 1.12				C* HCQ−	−0.08	0.91
	C	10 ± 0.92				HCQ+* HCQ−	0.25	0.43
1	HCQ+	9.92 ± 3.38	2.30	0.61	—	C* HCQ+	−1.25	0.11
	HCQ−	9.58 ± 4.04				C* HCQ−	−0.91	0.39
	C	8.67 ± 2.23				HCQ+* HCQ−	033	1
2	HCQ+	12.67 ± 6.2	13.06	<0.001*	0.12	C* HCQ+	−4.16	<0.001*
	HCQ−	11.33 ± 4.3				C* HCQ−	−2.83.	<0.01*
	C	8.50 ± 2.31				HCQ+* HCQ−	1.33	0.33
4	HCQ+	18.33 ± 7.22	49.03	<0.001*	0.35	C* HCQ+	−9.25	<0.001*
	HCQ−	17.33 ± 6.06				C* HCQ−	−8.25	<0.001*
	C	9.08 ± 2.34				HCQ+* HCQ−	1	0.99
6	HCQ+	20.75 ± 5.95	95.85	<0.001*	0.52	C* HCQ+	−10.16	<0.001*
	HCQ−	19.25 ± 3.99				C* HCQ−	−8.66	<0.001*
	C	10.58 ± 2.27				HCQ+* HCQ−	1.5	0.18
8	HCQ+	25.17 ± 6.76	124.33	<0.001*	0.58	C* HCQ+	−13.83	<0.001*
	HCQ−	23.58 ± 5.53				C* HCQ−	−8.12	<0.001*
	C	11.33 ± 2.58				HCQ+* HCQ−	1.58	0.30

C indicates control; HCQ, hydroxychloroquine; HCQ+, with a history of HCQ intake; HCQ−, without a history of HCQ intake; MD, mean difference; SD, standard deviation.

*indicates a statistically significant result with $p < 0.001$.

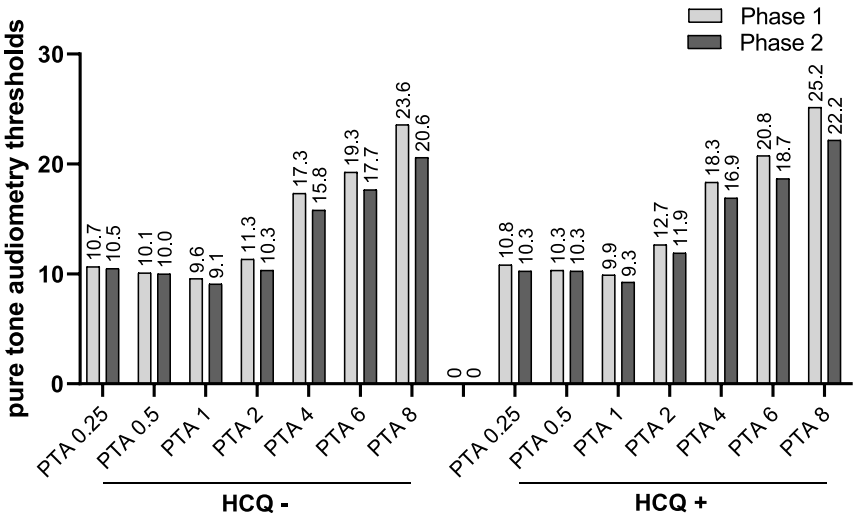

FIG. 1. Comparison of mean pure-tone audiometry thresholds at 0.25 to 8 kHz between the patients in the first phase (exactly at the end of the second) versus the second phase (1 mo later). HCQ indicates hydroxychloroquine; HCQ+, with a history of HCQ intake; HCQ–, without a history of HCQ intake.

SNR of OAE of the control group in the two phases 1 and 2 did not show a significant difference in all frequencies ($p > 0.1$ in all of them).

Audio-vestibular Symptoms

Table 3 shows the frequency and percentage of audio-vestibular symptoms reported in the patients in the first and second phases. Dizziness was the most common complaint, and imbalance and fullness were the least common symptoms in the first phase in the two groups of patients. The prevalence of symptoms decreased after 1 month from the initial evaluation.

DISCUSSION

Along with the most common otolaryngological findings as hyposmia/anosmia and hypogeusia/ageusia, otological/vestibular symptoms were reported during the COVID-19 pandemic. That suggested that the virus could affect the auditory and vestibular systems (16). At the same time, antivirals have been widely prescribed in the treatment of COVID-19 since the beginning of the pandemic. In several studies, concerns about some of these drugs have been reported and criticized (10). Hence, in the present study, we compared auditory system results and audiovestibular symptoms in COVID-19 patients between groups with and without a history of HCQ intake. We also compared these results with the control group (healthy individuals). The results showed poorer pure-tone thresholds at high frequencies (2, 4, 6, and 8 kHz) in both groups of COVID-19 patients and controls. Dependent results were also found for the SNRs of TEOAE, which was lower in patients at 2 to 5 kHz than in controls. Although the high-frequency hearing loss observed at pure-tone thresholds was mild in patients without medication, the low amplitudes of TEOAE supported the

TABLE 2. *Comparison of the signal to noise ratios in the transient evoked otoacoustic emission test at 1- to 5-kHz frequencies between patients with and without a history of hydroxychloroquine intake and the control group (n = 60 ears in each group)*

Frequency	Groups	Mean ± SD	*F*	*p*	Effect Size	Between Groups	MD	*p*
1	HCQ+	8.85 ± 2.47	3.53	<0.05	0.03	C* HCQ+	1.31	<0.05
	HCQ−	9.80 ± 3.54				C* HCQ−	0.36	>0.99
	C	10.16 ± 2.19				HCQ+* HCQ−	0.95	0.19
2	HCQ+	6.45 ± 2.63	30.79	<0.001*	0.25	C* HCQ+	3.96	<0.001*
	HCQ−	8.01 ± 3.35				C* HCQ−	2.40	<0.001*
	C	10.41 ± 2.27				HCQ+* HCQ−	−1.56	<0.01
3	HCQ+	4.01 ± 1.28	154.19	<0.001*	0.63	C* HCQ+	6.40	<0.001*
	HCQ−	4.96 ± 2.12				C* HCQ−	5.45	<0.001*
	C	10.41 ± 2.78				HCQ+* HCQ−	−0.95	≤0.05*
4	HCQ+	2 ± 1.33	235.78	<0.001*	0.72	C* HCQ+	6.88	<0.001*
	HCQ−	3.3 ± 1.27				C* HCQ−	5.75	<0.001*
	C	9.08 ± 2.64				HCQ+* HCQ−	1.13	<0.01
5	HCQ+	1 ± 1.13	394.36	<0.001*	0.81	C* HCQ+	7.05	<0.001*
	HCQ−	2.18 ± 1.11				C* HCQ−	5.86	<0.001*
	C	8.05 ± 1.99				HCQ+* HCQ−	1.18	<0.001*

C indicates control; HCQ, hydroxychloroquine; HCQ+, with a history of HCQ intake; HCQ−, without a history of HCQ intake; MD, mean difference; SD, standard deviation.

*indicates a statistically significant result with $p < 0.001$.

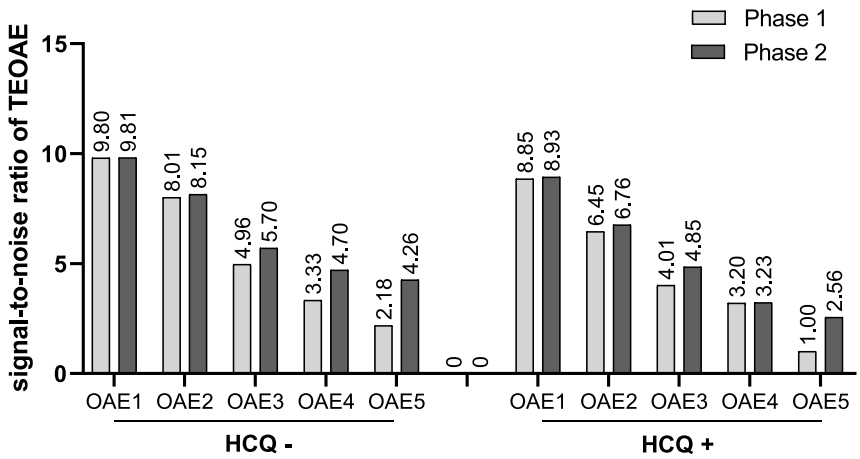

FIG. 2. Comparison of the mean signal-to-noise ratio of TEOAE at 1- to 5-kHz frequencies between the patients in the first phase (exactly at the end of the second) versus the second phase (1 mo later). HCQ indicates hydroxychloroquine; HCQ+, with a history of HCQ intake; HCQ–, without a history of HCQ intake; TEOAE, transient evoked otoacoustic emission.

hypothesis of damage to the cochlear structures after COVID-19. Our findings were consistent with the results of previous studies that also showed the destructive effects of COVID-19 on the cochlea (4,6,20). However, after several studies, the exact mechanism of its effect is still unknown. It is suggested that it may have a mechanism similar to other known viruses such as cytomegalovirus, rubella, and others. Therefore, this effect can be due to cochleitis with perilymphatic tissue involvement, and neuritis with vestibulocochlear nerve involvement that can lead to vertigo, tinnitus, hearing loss, and stress response resulting in the cross reaction of the inner ear antigens to viral infections. COVID-19 not only increases inflammatory processes in the cochlea and causes a cytokine storm but also can damage the hair cells, particularly those located in the basal portion of the cochlear (3,6,11,20–22). Moreover, ischemia and hypoxia of the cochlea and semicircular canals are other possible causes that can occur in different severities of COVID-19 (3,22). The results of previous studies suggest that the reduction in the OAE amplitudes and increased hearing thresholds may be due to the use of ototoxic drugs during the treatment of COVID-19, such as HCQ, which is widely administered (9). Hence, to evaluate the effects of the drug, we compared the two groups with and without HCQ; although there was no significant difference in PTA thresholds, the TEOAE amplitudes in the drug-treated group were statistically lower than in the nondrug group. TEOAE and distortion product otoacoustic emission tests are considered to be the gold standard in testing for ototoxicity (14). Hence, these findings could indicate the onset of effects on cochlear structures, especially OHCs, before they are reflected in audiometric results (18). However, the effect of HCQ on OHCs can depend on the dose and duration of use (11). In this study, 80% of the patients used HCQ for 5 days, and only two patients continued to take the drug for 6 days as symptoms persisted. The patients included in the present study did not have other comorbidities and therefore were not high-risk individuals who generally have more prolonged HCQ drug use for up to 10 days (15). All case reports that showed the destructive effects of HCQ on increasing PTA thresholds reported at least 1 month of HCQ use (10). Therefore, it seems that, as the results of this study, its short-term use is not necessarily associated with PTA threshold loss. In addition, the dose of HCQ used in our cases according to diagnostic and therapeutic flowcharts in our country was the lowest limit of the dose range recommended by the WHO (800–1,600 mg oral on the first day followed by 800 mg oral daily in one to three divided doses for 5 to 21 d) firstly (14).

In the second step, the tests were repeated 1 month later to check for progressive, irreversible effects or recovery in hearing results. Our findings showed lower auditory thresholds and greater OAE amplitudes in both groups of patients over time, indicating a relative improvement in the condition of the auditory system after 1 month of the initial

TABLE 3. *Frequency and percentage of symptoms related to hearing and balance reported by patients in the first phase versus second phase (n = 30 in each group)*

Type of Symptom	Frequency (%) in Phase 1 in Patients Treated With HCQ	Frequency (%) in Phase 1 in Patients Treated Without HCQ	Frequency (%) in phase 2 in Patients Treated With HCQ	Frequency (%) in Phase 2 in Patients Treated Without HCQ
Hearing loss	3 (10)	2 (6)	2 (6)	1 (3)
Vertigo	2 (6)	1 (3)	1 (3)	0
Dizziness	4 (13)	3 (10)	1 (3)	0
Imbalance	1 (3)	0	0	0
Tinnitus	4 (13)	2 (6)	2 (6)	1 (3)
Fullness	1 (3)	0	1 (3)	0

HCQ indicates hydroxychloroquine.

assessment. However, OAE amplitudes improved significantly in the drug-free group at high frequencies. Also, to ensure that the change in results in the patient group was not due to the retest, the tests were repeated in the second phase for the control group, which did not show a significant difference.

Unlike previous studies that reported the prevalence of dizziness and vertigo together, we tried to report the prevalence of these two entities separately by explaining the difference between true vertigo and dizziness and even imbalance without vertigo to the patients, because dizziness may not necessarily be related to the vestibular organ (1). In the first phase of the study, dizziness was the most frequent symptom in both HCQ-treated and nontreated patients (13 and 10%, respectively). In a meta-analysis conducted by Jafari et al. (3), the dizziness had a higher event rate than other symptoms in patients with COVID-19, with an event rate of 12.2 versus 3.1% for hearing loss and 4.5% for tinnitus. After 1 month, both groups reported a decrease in dizziness prevalence. As a result, only one of the seven patients who experienced dizziness in the first phase sustained the dizziness sensation in the second phase. Although three patients experienced true vertigo in the first phase, one patient reported this symptom along with a sensation of fullness during the second phase and was referred for further diagnostic testing. Hearing loss and tinnitus were the next two most often reported complaints, both of which recovered during the second phase. Our findings corroborated the finding of Hassani et al. (23), who reported that the audiovestibular symptoms resolved over time. Therefore, several audiovestibular complications reported during COVID-19 infection may be temporary. However, the reduction in symptoms over time may not be solely related to the auditory system (1,2). There seems to be a higher prevalence of audiovestibular symptoms in the COVID-19 group treated with HCQ than in the COVID-19 group that was not treated with HCQ. However, a larger sample size is required to make clear clinical conclusions. In all groups, only five patients (8%) reported hearing loss, and three of them continued to experience this sensation. The study's finding of slight hearing loss in COVID-19 patients illustrates that hearing loss can be a hidden impairment, emphasizing the critical necessity of hearing testing in these patients (1).

CONSIDERATIONS

Some factors influence the pharmacological effects of medications, including dosage, physical/chemical qualities, age, sex, genetic predisposition, and even the patient's general physiological state, which influences her/his ability to metabolize and hence eliminate the drug side effects. As a result, these considerations should be addressed when generalizing the findings of studies on pharmacological side effects. The effects of a drug could be affected by the presence of either of the other drugs. Therefore, co-administration of drugs can cause accumulation effects that could be caused toxicity, especially in the elderly (24). Multiple drugs are being used for the treatment of COVID-19, which can significantly increase serum CQ and HCQ. In particular, the combination of CQ and lopinavir/ritonavir is contraindicated (25). As a result, it is proposed that the ototoxic effects of HCQ in combination with other ototoxic medications be considered during the COVID-19 period, as well as in particular groups such as the elderly. Also, as mentioned, HCQ-induced hearing impairment can be reversible in some diseases such as rheumatoid arthritis (13). Therefore, long-term follow-up of participants in subsequent periodic hearing assessments seems useful in terms of a history of COVID-19 and HCQ consumption, which will be considered in our subsequent monitoring.

LIMITATIONS

This study did have several limitations, possibly because of additional confounding factors that were not considered. Because of the contagiousness of the disease, assessments could not be performed during the disease period, and assessments were performed 15 days after a positive polymerase chain reaction result. Patients' symptoms related to the audiovestibular system were recorded in a self-report manner, which may be associated with recall bias. Because of the patients' physical condition, particularly in the first phase, it was impossible to perform other clinical evaluations such as speech in noise perception (Quick SIN test), which may contribute to determining the transient toxic effects of using high doses of HCQ as a clinically significant finding. Another factor that could limit the achievement of clinically significant results in the hearing threshold between two groups of patients was the small sample size. The reason was strict entry conditions such as not taking other ototoxic drugs during COVID-19 treatment.

CONCLUSIONS

This study showed a slight hearing loss at high frequencies and the possibility of cochlear damage in COVID-19 patients with and even without HCQ intake compared with the healthy group. The SNRs of TEOAE were lower in patients with HCQ than in COVID-19 patients without this medication intake. Therefore, the results show that taking HCQ is probably associated with more OHCs damage. Its appearance is not seen in PTA thresholds with this dose of HCQ. Although a larger sample size and some clinical assessments such as speech perception in noise that can be sensitive to the effects of ototoxicity might help achieve clinically significant results between patient groups. Also, the ototoxicity effect of high loading doses of HCQ use in the COVID-19 patients should be considered even in patients who do not report audiovestibular symptoms due to hidden hearing loss probability. Follow-up of patients in both groups showed that hearing thresholds and OAE amplitudes were partially reversible over time. Dizziness, tinnitus, and hearing loss were the most commonly reported symptoms, respectively, but their prevalence decreased over time.

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