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Research Article

Impact of SARS-CoV-2 Treatment on Development of Sensorineural Hearing Loss

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Abstract: Ototoxicity had been a known viral manifestation. This raised the possibility for the current pandemic caused by the novel coronavirus to induce temporary or permanent auditory manifestations. The struggle to search for therapeutic options to counter the pandemic is still underway. Meanwhile, the management had relied on using antimalarials and antivirals; which themselves have proven ototoxic repercussions. Interestingly this brings to a point of further debate whether the auditory dysfunction is induced by the virus alone or by the drugs that are used to pacify the pathology of the viral exhibition or both. This article will channel this current implication of the hearing loss debate focusing on the mainstay regimen for SARS-CoV-2 management. A bibliographic search was performed to review current literature in scientific databases PubMed, Research Gate, and Google Scholar. Published articles encompassed within our inclusion criteria were reviewed thoroughly to draw possible outcomes. Reported SARS-CoV-2 manifestations are sensorineural hearing loss with disturbed vestibulo-auditory symptoms. Reviewed research data suggested aggravation in ototoxicity induced by these medications. This upsurges the controversies surrounding the safety and efficacy of the medications currently in active use for managing SARS-CoV-2 infection. Further therapeutic strategies need to be researched for equipping the arsenal to effectively treating SARS-CoV-2 and its complications.

Keywords: SARS-CoV-2, COVID-19, toxicity, sensorineural hearing loss, antimalarials, anti-virals

1. INTRODUCTION

Hearing loss following viral infection has been reiterated for years. Viral-induced hearing loss is known to have mild to profound impact, being either unilateral or bilateral and conductive or sensorineural in type [1]. The patient presentations differ as per the type of viral infection and the pathology that follows; be it direct or indirect damage to the anatomical structures of the inner ear or means to activation of the host immune system to inflict damage to the hearing apparatus [2]. Of note here is the ototoxic potential of medications that are being used to counter the viral pandemic at hand [3].

The outbreak of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, along with its predecessors [SARS-CoV-1 and Middle East respiratory syndrome (MERS)], have had life-threatening consequences [4]. The SARS-CoV-2 symptoms may appear as early as 2 days or may extend up to 14 days after viral exposure [5]. Olfactory and gustatory symptoms are the key findings of the SARS-CoV-2 virus apart from respiratory, cardiologic, and GIT symptomatology [6]. Current literature also hints at neurotrophic and neuroinvasive features with SARS-CoV-2 infection [7]. By extension, the role of SARS-CoV-2 as a causative agent in hearing loss has recently been noted and has ignited researchers to investigate and collate updated evidence available on the prevalence of hearing loss in SARS-CoV-2 infected patients.

Finding this possible link between SARS-CoV-2 to hearing loss has become relevant as to what medicament plan do we offer to counter

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SARS-CoV-2; would it predispose the individual to further the hearing loss impairment? Currently, multiple off-label anti-virals and antimalarials such as lopinavir-ritonavir, hydroxychloroquine, chloroquine, and certain other drugs are used in preference for the early treatment of SARS-CoV-2 [8]. Prescribing medications with possible targets against the SARS-CoV-2 virus, having a lack of pharmacokinetic and pharmacodynamic implications was similar to shooting in the dark, which resulted in several unwanted consequences that added further dilemma to the pandemic scenario. Lack of therapeutic options against SARS-CoV-2 could be identified from the fact that even with randomized control trials pointing the insignificant effect of antimalarial drug-like hydroxychloroquine on death and recovery rate in SARS-CoV-2; along with other antimalarial and antiviral drugs are still under consideration in health care centers across the world [9-11]. One of the unwanted consequences is ototoxicity which interestingly had been a shared adverse effect to most of the available therapeutic arsenal against SARS-CoV-2; including antibacterial, anti-inflammatory, antimalarials, anti-virals, and certain immunomodulatory compounds [12, 13].

Ototoxicity is defined as hearing impairment, tinnitus, and imbalance caused by damage to the inner ear structure and vestibular system which could result in a temporary and/or permanent hearing disability [14]. Chloroquine and hydroxychloroquine had previously been sought for the findings of auditory dysfunction such as sudden sensorineural hearing loss, vertigo, and tinnitus in patients treated with these anti-malarial drugs [11, 15]. In chronic cases, the symptoms got worse and irreversible based on how long the therapy continues [16]. In some clinical settings, anti-malarial drugs were prescribed in combination with an antibiotic like Azithromycin, to increase the therapeutic effectiveness in SARS-CoV-2 patients. Unfortunately, the combination of drugs could potentiate mild to severe audiological manifestations based on the duration of exposure [17].

Hearing loss has detrimental effects on quality of life, depending on the age of onset as it impinges on cognitive skills, learning abilities, and results in an invisible handicap of the affected person with severe psychological solitary confinement [18]. Tinnitus increases the risk of anxiety and depression. In addition, inner ear pathology leading to spatial disorientation increases the chances of physical injury and also leads to poor productivity with social isolation [19-21]. The hearing loss still does not have standard care and has limited pharmacologic modalities [15]. The purpose behind this study is to collate the impact of SARS-CoV-2 and the currently used medications; to signify the ototoxic impact that could be generated with a charged focus on neurologic inferences such as sensorineural hearing loss (SNHL). This would help direct our attention towards risk mitigation and limiting strategies for current SARS-CoV-2 therapeutics to avert unwanted outcomes.

2. MATERIALS AND METHODS

The systematic literature search was performed primarily on three databases: PubMed, Research Gate, and Google Scholar engines on 24th February 2021 to identify pertinent literature to our study question, as presented in Figure 1. The search strategy was based on the MeSH words: COVID-19, SARS-CoV-2, ototoxicity, tinnitus, hearing loss, antiviral and antimalarial medications.

Automated database search provided 59 articles with an addition of another research paper by bibliographic hand search, cumulating to a total of 60 articles. Repeated articles were removed manually. Studies that focused on therapeutic implications of SARS-CoV-2 along with ototoxic complications formed the basis of our inclusion criteria and 21 papers were identified for further screening for inclusion in our systematic review. These research articles were based on different study categories i.e. clinical reports, case studies, case reports, and cross-sectional studies. Studies with insufficient findings, inconclusive data, and non-English publications were excluded from our article. On thoroughly reviewing the filtered papers, key findings were extracted for further analysis.

3. RESULTS AND DISCUSSION

Steering the therapeutic realm of coronavirus SARS-CoV-2 infection is currently reliant on symptomatic treatment and supportive care. The development and issuance of vaccines are a time-consuming and

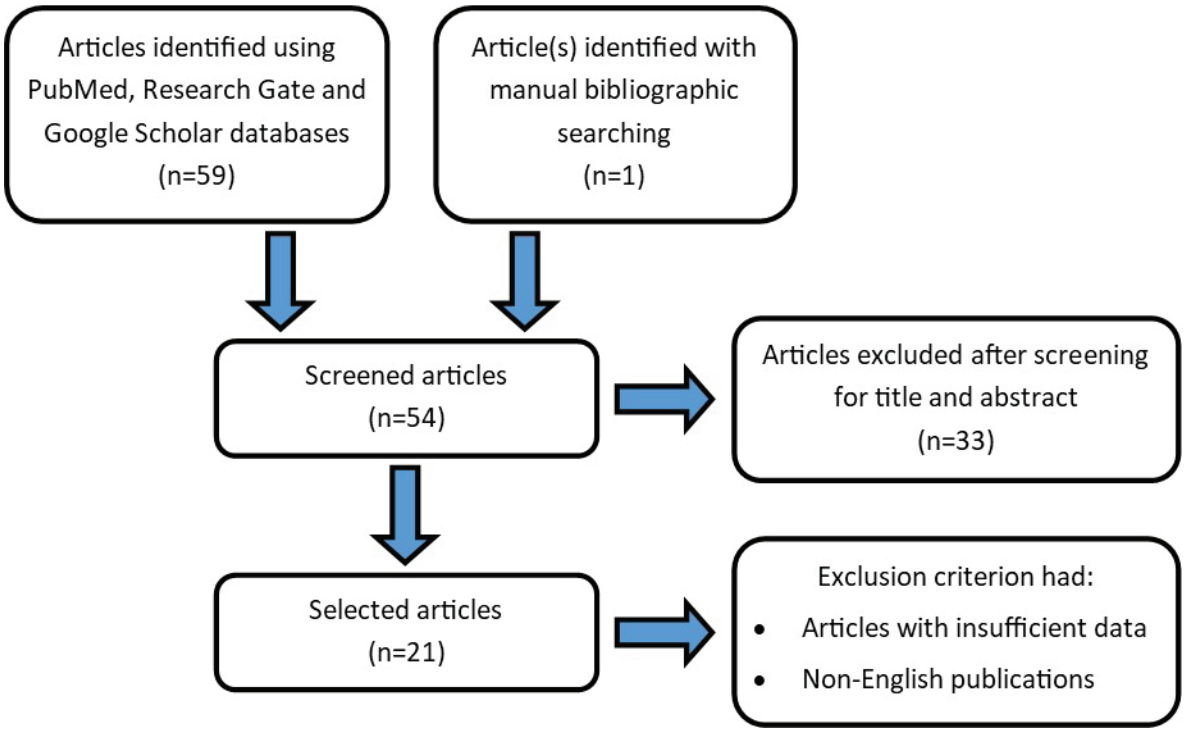

Fig. 1. Flow diagram of the study selection process.

expensive modality, which is currently underway. To curtail the spread of the infection, the logical introduction of antiviral medications along with repurposed anti-malarial drugs was maintained, as the initial management strategy. Even though these medications had previously been studied for their pharmacotherapeutic influence, but their safety profile under the current coronavirus pandemic still needed further clinical evidence. A comprehensive list of drugs, summarized in table 1, was compiled including antimalarials, anti-virals, antibiotics, immunomodulatory agent, and their combinations. One of the enthusiastic approaches taken to manage SARS-CoV-2 was to prescribe antimalarials - chloroquine and hydroxychloroquine. Since limited therapies are available for possible SARS-CoV-2 management. A study on chloroquine revealed that it might block SARS-CoV-2 viral replication by elevating endosomal pH followed by a decrease in viral load; identifying antimalarials to be in vogue [23]. Interestingly, randomized control trials on hydroxychloroquine had been published that showed no impact on improving SARS-CoV-2 infection mortality [22]. This confronted the FDA-approved Emergency Use Authorization (EUA) of chloroquine and hydroxychloroquine, which had been placed during the early days of the pandemic. However, the agency reversed its approval due to new information obtained from clinical trials that reported confounding results. Various studies reported adverse impacts on the heart, ears, skin, eyes, and muscles in patients treated with chloroquine and hydroxychloroquine [24-27]. FDA issued a warning in April 2020 regarding hydroxychloroquine use in non-research and off-label health care settings due to these emergency safety concerns (1).

The scarcity of available pharmacologic options still upholds the consideration of antimalarials for therapy. This trend engages the ototoxic impact of chloroquine and hydroxychloroquine use that could include reversible and irreversible symptoms of tinnitus, SNHL, and vertigo. Various studies revealed either atypical audiograms or loss of hearing ability in SARS-CoV-2 positive patients treated with chloroquine. Some reported cases had short-term SNHL after chloroquine treatment while this condition was improved after cessation of treatment [28, 29]. Dwivedi and his coworker

Table 1. List of currently used therapeutics for SARS CoV-2 with related ototoxic implications.

Category	Medication	Type of Hearing Loss	Drug Effect	Other Symptoms	Range of Hearing Loss	Laterality	References
Anti-Malarial	Chloroquine	SNHL	Both	Tinnitus and Vertigo	Severe	Bilateral	[69-71]
	Hydroxychloroquine	SNHL	Both	Tinnitus	Mild to Severe	-	[72, 73]
	Lopinavir–Ritonavir	-	Reversible	-	Moderate	Bilateral	[74, 75]
Anti-Viral	Ribavirin	SNHL	Both	Tinnitus	Severe	Unilateral	[47, 49, 76]
	Ivermectin (also anti-parasitic)		Reversible	Vertigo and Dizziness	-	-	[49]
Non-Steroidal Anti-Inflammatory Drugs	Aspirin	-	Reversible	Tinnitus and Vertigo	-	Bilateral	[77-80]
	Indomethacin	-	Reversible	Tinnitus and Vertigo	-	-	[77, 80]
	Naproxen	-	Irreversible	-	-	-	[80]
	Ibuprofen	-	Irreversible	Tinnitus and Vertigo	-	-	[77, 80]
Antibacterial	Azithromycin	SNHL	Both	Tinnitus and Vertigo	Mild to Severe	Bilateral	[14, 81]
Immunomodulators	Interferons (IFNs)	SNHL	Reversible	Tinnitus	-	Bilateral	[49, 62, 63]

*SNHL= Senserineural Hearing Loss

reported a case of 52 years old male experiencing bilateral permanent deafness followed by blurring of vision and vertigo after a single dose of chloroquine [30]. In another study, 13 out of 70 patients treated with chloroquine experienced reversible cochlear injury despite normal tone audiogram outcomes detected by brainstem audiometry [31]. Likewise, permanent severe SNHL cases have also been reported [30-32]. Similar to chloroquine, hydroxychloroquine treatment also produced ototoxicity in reported cases. Reversible SNHL was observed after hydroxychloroquine administration along with irreversible cases [33-36]. Tinnitus is also described together with loss of hearing in a few cases [34, 35].

The SNHL or tinnitus was observed to manifest much earlier after chloroquine use rather than hydroxychloroquine where prolonged administration was recognized. The recommended chloroquine dose for SARS-CoV-2 patients is 1g for 10 days that is extensively higher than the acclaimed dose for treatment of malaria (1g for 3 days) [37]. Furthermore, the suggested hydroxychloroquine dose for SARS-CoV-2 patients is 800 mg, which is later reduced to 400 mg for 4 days [38]. Another study recommends giving hydroxychloroquine at 600mg for 10 days. Although proposed doses of hydroxychloroquine and chloroquine for SARS-CoV-2 patients are considerably higher than suggested for malarial patients, similarly duration of use also influences the possible development of side effects. Even with numerous reports on chloroquine and hydroxychloroquine-induced hearing loss are established and FDA aims to restrict their use; very limited research exists on SARS-CoV-2 patients, permitting clinical reluctance on restraint [39].

The antivirals considered for managing SARS-CoV-2 include antiretrovirals and non-antiretrovirals. The antiretrovirals include Nucleoside Reverse-Transcriptase Inhibitors (NRTI) and Protease inhibitors. These drugs may develop adverse outcomes with different frequencies and intensity based on the active cellular mechanism being involved such as NRTI causes mitochondrial toxicity that leads to hearing impairment [40]. In one Australian longitudinal study, a positive association of NRTI treatment disposing to hearing loss has been evidenced in HIV-positive patients. Another

study reported a positive association between hearing impairment and mitochondrial dysfunction with protease inhibitor therapies in a 44 years old male patient [41]. As per available literature, the duration of anti-retroviral therapy could predispose to hearing impairment while some studies did not find any adverse effects on hearing loss after using the therapy for a longer duration [42].

The protease inhibitors such as lopinavir alone and/or in combination with ritonavir have proven in-vitro inhibitory activity against SARS-CoV-1, SARS-CoV-2, and MERS [43]. This had been a widely prescribed drug combination for the treatment of SARS-CoV-2 based on in-vitro experiments, preclinical cases, and observational reports. Lopinavir is the main component in the inhibition of SARS-CoV-2 target protein and along with ritonavir; it potentiates the efficacy of lopinavir by elevating its half-life. Lopinavir–ritonavir inhibits the highly conserved protease of SARS-CoV-2; thereby inhibiting viral replication in the host body and decreases the viral load. It has proven neurotoxic effects which results in bilateral SNHL with depressive symptoms when used for extended periods. Hearing reverts back to normal following discontinuation of the drug regimen [44].

Ribavirin targets viral replication by inhibiting viral mRNA synthesis. This antiviral agent is used in combination with interferons for SARS-CoV-2 treatment [45]. Apart from its significant therapeutic potential in SARS-CoV-2 treatment it also holds proven literature on ribavirin-induced ototoxicity. A recent study has shown a severe sudden hearing loss in patients who received combined therapy of ribavirin and interferons, with a reversible and irreversible impact [46-49]. Due to the scarcity of research data, it is still unknown that either ribavirin is the sole reason behind sensorineural hearing loss or is it due to the effect of combining multiple drugs [50].

Ivermectin is a broad-spectrum anti-parasitic drug that has also shown to actively inhibit viral replication in SARS-CoV-2 patients [51]. Although very limited studies are available on ivermectin-induced ototoxicity the available data has suggested vestibuloauditory manifestations of ivermectin therapy [52]. It is used alone and also in combination with other drugs like ribavirin, chloroquine, and hydroxychloroquine [53].

The use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) such as aspirin was directed to reduce the inflammatory condition from developing, in addition to dealing with headache and possible body ache. Aspirin can induce reversible ototoxicity and causes high-frequency tinnitus. It has been noted to produce a temporary effect on sensory cells of the inner ear, whilst the pathogenesis is still not clear [54]. Other NSAIDs such as ibuprofen and naproxen produce irreversible hearing impairment but have a lower incidence rate as compared to aspirin [55].

Azithromycin is widely used to treat bacterial infection and the human influenza virus [56, 57]. It is used in combination with hydroxychloroquine and lopinavir-ritonavir; as a three-drug combination with greater efficacy [58]. This triple therapy was observed to be very effective as lopinavir-ritonavir with azithromycin elevates blood serum levels of hydroxychloroquine, effectively targeting the virus but also predisposes to ototoxicity [59].

Interferons (IFNs) are signaling proteins such as interferon-α (IFN-α) and interferon-β (IFN-β), with antiviral and immunomodulatory efficiencies [58]. Research on clinical data with COVID-positive patients reveals IFN-α therapy to clear the viral load by decreasing inflammatory biomarkers [60, 61]. Nevertheless, both in-vivo and in-vitro studies have confirmed the ototoxic impact of IFNs therapy. In one study, participants who were on IFN-α or IFN-β therapy; 35% later developed SNHL (18/49 patients) and 29% developed tinnitus (14/49 patients) [61]. In another study, 37% of total study patients documented SNHL when treated with IFNs [62]. Hearing loss associated with IFNs therapy is reverted to normal upon discontinuation of therapy within two weeks [63]. Animal models suggested cochlear damage but the exact mechanism of IFNs induced hearing loss is still not clear [64].

Therapeutics of SARS-CoV-2 involves a combination of drugs, and recent research data supports the proposition of synergistic audiovestibular function when multiple ototoxic SARS-CoV-2 drugs are co-administered for the treatment purpose [15]. Currently, the most commonly presented combinations are

hydroxychloroquine with lopinavir-ritonavir or IFNs, azithromycin, and ivermectin, lopinavir-ritonavir, IFNs, and ribavirin. There is insufficient data available that could point out the possible mechanistic of ototoxic synergism of these therapies [59]. In addition, several compounding factors also exist that increases the chance of acquiring this induced ototoxicity such as age, underlying impaired hearing function, hereditary component, and impaired drug elimination function [65]. Kidney function is suspected to affect up to 20% to 40% in SARS-CoV-2 patients and results in a disturbing drug elimination process [66]. It will lead to the elevated serum ototoxic therapeutics level of drugs like hydroxychloroquine, chloroquine, and ribavirin [65]. In aged individuals, as the renal elimination system deteriorated with time so they are more prone to develop ototoxicity when exposed to these medications [67]. Similarly, individuals with underlying hearing disability or having a positive family history of hearing loss are at a higher susceptibility to develop ototoxic complications when they use these drug combinations [68].

Clinical improvisation is needed to screen the serum level of these potential ototoxic therapeutics in people at risk including high-risk populations to overcome the lifelong consequences of these drugs on hearing and balance functioning [65].

4. CONCLUSION

The SARS-CoV-2 pandemic has added a lot of pressure over the therapeutic domain to challenge the evolving nature of SARS-CoV-2 viral infection. Available research data on SARS-CoV-2 therapeutics have shown symptomatic improvement with raised possibility of ototoxic impact with these proposed therapeutic interventions. With an active rise in SARS-CoV-2 cases, patients unknowingly were exposed to these ototoxic medications. It is therefore of utmost importance that the healthcare services should vigilantly assess the symptoms of hearing impairment, tinnitus, and vertigo; to prevent lifelong health consequences. Further research needs to be directed to search for alternate medications which would help mitigate the viral infection and would thereby avert the ototoxic impact of currently used therapies and help prevent long-term disability.

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6. CONFLICT OF INTEREST

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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