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Assessment of auditory function in hepatitis "C" patients managed by combination of sofosbuvir and daclatsavir

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Abstract

Background: To evaluate the effect of daclatasvir and sofosbuvir on auditory function in hepatitis C patients. Thirty hepatitis C virus (HCV) patients were included in this study with age ranged from 22 to 55 years. All patients underwent full audiological evaluation before beginning and after completion of their treatment with combination of daclatasvir and sofosbuvir.

Result: When the results of audiological data were compared before and after treatment, we found that; there were statistically significant differences in the pure tone audiometry (PTA) threshold and ART bilaterally mainly in the high frequency region. Transient evoked otoacoustic emission (TEOAE) reproducibility showed a statistically significant difference bilateral. However, there was no statistically significant difference in the Auditory Brainstem Response (ABR) findings.

Conclusion and recommendations: The combination therapy of daclatasvir and sofosbuvir used in patients with HCV led to deterioration in the hearing threshold in the basic audiological tests (PTA and immitancemetry). In addition, it had an adverse effect on the cochlear OHCs, with no affection on auditory nerve, brain stem functions or in sub-thalamic function, it seems that it had no effect, we cannot confirm. The study evaluate hearing at the end of treatment immediately. We recommend performing a routine monitoring of auditory functions in HCV patients treated with daclatasvir and sofosbuvir combination by specialist for early detection of auditory changes to avoid further damage to auditory system.

Keywords: Hepatitis C, Sofosbuvir-daclatsavir, Audiometry, OAE, ABR

Background

Hepatitis "C" is a serious disease affecting the liver. It is caused by infection with hepatitis "C" virus (HCV) that is an enveloped virus with a single-stranded ribonucleic acid (RNA) genome a member of the flaviviridae family and genus pepacivirus [1]. The main routes of transmission of HCV are blood transfusions, medical procedures, sharing drugs and needles, sexual transmission, and maternal transmission [2]. There are different lines for treatment of HCV as Peginterferon alfa-ribavirin treatment which is effective in 40% of genotype 1 HCV and 75% of genotype 2 or 3. One of side effects of pegylated interferon/ribavirin is hearing loss which was insidious and unilateral; however it was reversible after discontinuation of interferon [3, 4]. New avenue line of HCV treatment is the combination between daclatasvir and sofosbuvir that have potent antiviral activity and broad genotypic coverage. According to the researchers, best knowledge the study of relationship between

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HCV patients treated with this combination and hearing affection not yet done. So, the rationale of this study is to assess the auditory function of HCV patients before and after treatment with daclatasvir and sofosbuvir combination [2].

The rationale of our study was to evaluate the early effect of daclatasvir and sofosbuvir on auditory function in hepatitis C patients.

Patients and methods

Patients

Thirty HCV patients were included in this study with age ranged from 22 to 55 years. They were selected from the digestive system hospital and the audiological evaluations were done at Audio-Vestibular Unit, Sohag University Hospital, in the duration from March 2017 to September 2018. All patients were examined before and after completion of their treatment with combination of daclatasvir and sofosbuvir. The duration of their treatment was 3 months. Any patients with complain as regards hearing was excluded from the study. The first plane of our research was 100 patients within one and half year. However, the net participants were 30 as many of them were excluded either because of refusing to do audiological evaluation, or did not complete the course of treatment, or did not come in follow-up sessions.

Method

All the patients included were subjected to the following procedures:

1. Full history taking:

Including personal history, history of hearing loss, tinnitus, vertigo, history to exclude any otological or neuro-otological diseases.

2. Clinical examination:

Including otologic examination and abdominal examination.

3. *Basic audiologic evaluation:* done in a sound treated room.

    a. Pure tone audiometry: were measured using a calibrated Amplaid 309 clinical audiometer. Air conduction thresholds were measured for frequencies from 250 to 8000 Hz using Telephonics TDH39 earphones. Bone conduction thresholds were obtained for frequencies from 250 to 4000 Hz using a Radio Ear B71 bone vibrator. The audiometric thresholds were measured using the modified Hughson-Westlake method.
    b. Speech audiometry: speech reception threshold (SRT), using Arabic spondaic words [5]. Word discrimination score (WDS), using Arabic phonetically balanced (PB) words [6].
    c. Immitancemetry: low-frequency tympanometry with a probe tone of 226 Hz and testing of the acoustic reflex threshold (ART) using pure tones at frequencies 500, 1000, 2000, and 4000 Hz.

4. TEOAEs:

For assessment of cochlear outer hair cells. It was elicited using non-linear click stimuli at stimulus intensity ranges from 80 dB peak equivalent sound pressure level (SPL), 80 μs duration, at a rate of 50 clicks per second, within a time window of 20 ms. TEOAEs were analyzed by recording 260 sweeps in one session and averaged within 5 frequency bands centered at (1, 1.5, 2, 3, and 4 kHz). Responses were represented by an average of a maximum of 260 click stimuli trains (1040) stored into two different buffers averaged separately (A and B) for a total of 2080 clicks. The averaged amplitude in dB, of these two waveforms presented the overall echo level in dB SPL. In addition, the reproducibility of TEOAEs was tested by the correlation between signals from the two buffets. All responses were stored for analyses. An acceptable TEOAE is 3 dB above the noise floor and is reproducible [7]. Those who showed an overall 3 reproducibility of 70% were described to have a PASS result and those with < 70% but still had > 50% were considered to have a present TEOAE and were described to have a Partial PASS result, as they did not show a pass criterion on all the tested frequency bands [8].

5. Auditory Brainstem Response test (ABR):

For assessment of the function of the auditory nerve and low brainstem.

    a. Stimulus parameters:

    (i) Type: rarefaction acoustic clicks with a duration of 100 ms. (ii) Filter: 150–3000 Hz (iii) Time window: 10 ms. (iv) Intensity: 90 dB n HL (v) Number of sweeps: 1000 sweeps. (vi) Rate: low repetition rate (LRR) at 21.1 pulse/s and high repetition rate (HRR) at 100 pulse/s.
    b. Identification of response: the following measurements were calculated; absolute latencies of wave I–III and V: wave I at 1.6 ms, wave III at 3.6 ms

and wave V at 5.6 ms, and interpeak latencies I–III, III–V, and I–V at regular repetition rate. Also, absolute latency of wave V at high repetition rate was recorded. Stimuli were presented monaurally to both ears via a head phone TDH39 starting with right ear. The test procedure was explained to all participants, during test acquisition, every participant was instructed to lie down calmly on a comfortable coach [9].

6. Daclatasvir and sofosbuvir combination course:

Patients eligible for treatment received sofosbuvir 400 mg and daclatasvir 60 mg daily for 12 weeks and were assessed for sustained virologic response at 12 weeks following the end of treatment (SVR 12).

Re-evaluation of the auditory functions after completion of the combination course

Statistical analysis

Data were analyzed with SPSS Version 21. Qualitative data were described using number and percent while continuous variables were presented as mean ± standard deviation (SD). The differences between pre and post-treatment audiological measures were compared using paired *t* test. A *p* value of < 0.05 was considered statistically significant and of < 0.001 was considered as being highly significant.

Results

This study was conducted on 30 patients with HCV. They were 15 males and 15 females. Their age ranged from 22 to 55 years with the mean 41.4 ± 9.9 years. As regards

Table 1 PTA, SRT, WDS, ART, TOAE, and ABR findings for both ears before treatment

Item	Frequency	Right ear	Left ear
PTA	**250 Hz**	11.33 ± 2.25	13.83 ± 3.13
	500 Hz	14.00 ± 2.25	14.00 ± 2.75
	1 kHz	17.50 ± 2.25	15.00 ± 3.94
	2 kHz	15.50 ± 4.42	17.00 ± 4.66
	4 kHz	15.63 ± 3.96	15.00 ± 4.15
	8 kHz	15.67 ± 4.10	14.50 ± 3.31
SRT		15.00 ± 3.71	14.03 ± 4.52
WDS		98.13 ± 2.03%	98.80 ± 1.86%
Acoustic reflex threshold (ART)	500 Hz	86.83 ± 6.42	88.50 ± 6.04
	1 kHz	87.67 ± 7.16	87.67 ± 7.16
	2 kHz	89.67 ± 7.98	89.67 ± 7.98
	4 kHz	92.00 ± 7.13	89.83 ± 7.13
TOAE	0.75–1.25 kHz	10.29 ± 4.05	9.53 ± 4.50
	1.25–1.75 kHz	14.64 ± 6.53	15.62 ± 7.28
	1.75–2.50 kHz	13.96 ± 6.48	13.62 ± 4.70
	2.50–3.50 kHz	12.53 ± 6.74	10.32 ± 4.89
	3.50–4.50 kHz	8.40 ± 4.31	12.47 ± 3.07
	Overall	11.21 ± 4.75	13.32 ± 8.60
TOAE reproducibility (%)	0.75–1.25 kHz	80.07 ± 14.30	79.20 ± 16.48
	1.25–1.75 kHz	85.83 ± 18.59	89.13 ± 13.53
	1.75–2.50 kHz	87.03 ± 13.73	88.43 ± 13.10
	2.50–3.50 kHz	81.03 ± 15.78	78.23 ± 19.03
	3.50–4.50 kHz	72.40 ± 14.70	75.30 ± 15.37
	Overall	79.60 ± 17.72	78.83 ± 14.77
ABR, LRR	Wave I	1.71 ± 0.20	1.85 ± 0.10
	Wave III	3.90 ± 0.18	3.98 ± 0.23
	Wave V	5.71 ± 0.18	5.72 ± 0.18
	Inter peak I–III	2.19 ± 0.24	2.10 ± 0.19
	Inter peak III–V	2.21 ± 0.04	1.75 ± 0.17
	Inter peak I–V	4.01 ± 0.23	3.87 ± 0.21
ABR (HRR)	Wave V	5.99 ± 0.30	5.99 ± 0.27

the duration of the disease, it ranged from 3 months to 3 years and the mean was 1.05 ± 0.903 years. 50% of our patients were housewives, 26.7% were farmers, 20% were workers, and 1 (3.3%) patient had no work. No patient had any complaint as regards hearing and no patient was under proton pump therapy.

In our study, we did audiological evaluation for HCV patients before they started their treatment and after end of treatment with sofosbuvir and daclatsavir.

Table 1 summarizes the audiological findings before treatment with combination of sofosbuvir and daclatsavir. All patients had bilateral normal hearing sensitivity at all frequencies and within normal TEOAEs and ABR findings.

Table 2 showed the audiological findings of the right ear after treatment with sofosbuvir and daclatsavir compared to the baseline measures. This table showed that there were statistically significant differences between the two measures regarding PTA at 2, 4, and 8 kHz; ART at 4 kHz; TOAE reproducibility at 2.5–3.5 and 3.5–4.5 kHz; and a highly significant difference regarding TOAE reproducibility at 1.75–2.5 kHz. However, there was no statistically significant difference in the ABR findings of the right ear before and after treatment.

Table 3 showed the audiological findings of the left ear after treatment with sofosbuvir and daclatsavir compared to the baseline measures. This table showed that there were statistically significant differences between the two measures regarding PTA at 4 kHz; ART at 4 kHz; TOAE reproducibility at 0.75–1.25, 1.25–1.75, 2.5–3.5, and 3.5–4.5 kHz; and a highly significant difference regarding PTA at 8 kHz and ART at 500 Hz. There was no statistically significant difference in the ABR findings of both ears before and after treatment.

Table 2 PTA, SRT, WDS, ART, TOAE, and ABR of the right ear before and after treatment

Item	Frequency	Pre	Post	*T* test	*P* value
PTA	**250 Hz**	11.30 ± 2.25	11.17 ± 3.11	0.22	0.83
	500 Hz	14.00 ± 2.75	13.33 ± 3.56	1.07	0.29
	1 kHz	17.50 ± 4.10	16.67 ± 5.47	1.22	0.23
	2 kHz	15.50 ± 4.42	17.33 ± 4.69	2.26	**0.03***
	4 kHz	15.83 ± 3.96	17.50 ± 6.66	1.26	**0.03***
	8 kHz	15.67 ± 4.10	18.50 ± 8.53	2.38	**0.02***
SRT		15.00 ± 3.71	15.33 ± 3.93	0.70	0.49
WDS		98.13 ± 2.03%	97.40 ± 2.23%	1.44	0.16
ART	500 Hz	86.33 ± 6.42	86.83 ± 5.80	1.14	0.26
	1 kHz	87.67 ± 7.16	87.67 ± 6.80	0.00	1.00
	2 kHz	89.67 ± 7.98	89.67 ± 7.76	0.00	1.00
	4 kHz	89.83 ± 7.13	92.00 ± 8.67	2.36	**0.03***
TOAE	0.75–1.25 kHz	10.29 ± 4.05	12.06 ± 6.12	1.62	0.12
	1.25–1.75 kHz	14.64 ± 6.53	15.78 ± 6.69	1.09	0.28
	1.75–2.50 kHz	13.96 ± 6.48	12.95 ± 9.10	1.01	0.32
	2.50–3.50 kHz	12.53 ± 6.74	10.25 ± 7.06	1.60	0.12
	3.50–4.50 kHz	8.40 ± 4.31	7.92 ± 3.50	0.47	0.64
	Overall	11.21 ± 4.75	11.23 ± 5.57	0.02	0.99
TOAE reproducibility (%)	0.75–1.25 kHz	80.07 ± 14.30	76.63 ± 24.15	0.92	0.37
	1.25–1.75 kHz	85.83 ± 18.59	90.37 ± 11.07	1.70	0.10
	1.75–2.50 kHz	87.03 ± 13.73	70.30 ± 2.85	3.66	**< 0.001****
	2.50–3.50 kHz	81.03 ± 15.78	68.00 ± 5.86	2.75	**0.01***
	3.50–4.50 kHz	72.40 ± 14.70	61.13 ± 5.63	1.75	**0.03***
	Overall	79.60 ± 17.72	77.40 ± 19.70	0.81	0.42
ABR, LRR	Wave I	1.71 ± 0.20	1.71 ± 0.23	0.14	0.89
	Wave III	3.90 ± 0.18	3.97 ± 0.21	3.21	0.90
	Wave V	5.71 ± 0.18	5.93 ± 0.26	3.72	0.87
	Inter peak I–III	2.19 ± 0.24	2.26 ± 0.29	1.82	0.76
	Inter peak III–V	2.21 ± 0.04	1.96 ± 0.32	0.63	0.53
	Inter peak I–V	4.01 ± 0.23	4.22 ± 0.32	3.74	0.84
ABR (HRR)	Wave V	5.99 ± 0.31	6.13 ± 0.44	1.88	0.07

There were statistically significant differences between the two measures regarding PTA, AR, and TEOAE

Table 3 PTA, SRT, WDS, ART, TOAE, and ABR of the left ear before and after treatment

Item	Frequency	Pre	Post	*T* test	*P* value
PTA	**250 Hz**	13.83 ± 3.13	13.50 ± 2.98	0.49	0.63
	500 Hz	14.00 ± 2.75	13.33 ± 3.56	1.07	0.29
	1 kHz	15.00 ± 3.94	15.67 ± 5.83	0.55	0.59
	2 kHz	17.00 ± 4.66	16.33 ± 3.93	1.16	0.26
	4 kHz	15.00 ± 4.15	17.67 ± 7.04	1.92	**0.04***
	8 kHz	14.50 ± 3.31	21.17 ± 8.48	4.49	**< 0.001****
SRT		14.03 ± 4.52	15.17 ± 2.78	1.42	0.17
WDS		98.80 ± 1.86%	98.27 ± 2.02%	2.11	0.24
ART	500 Hz	88.50 ± 6.04	90.50 ± 5.31	3.89	**< 0.001****
	1 kHz	87.67 ± 7.16	87.67 ± 6.79	0.00	1.00
	2 kHz	89.67 ± 7.98	89.67 ± 7.76	0.00	1.00
	4 kHz	89.83 ± 7.13	92.00 ± 8.67	2.36	**0.03***
TOAE	0.75–1.25 kHz	9.53 ± 4.50	8.53 ± 3.98	0.67	0.51
	1.25–1.75 kHz	15.62 ± 7.28	16.56 ± 9.72	0.67	0.51
	1.75–2.50 kHz	13.62 ± 4.70	13.88 ± 5.60	0.38	0.71
	2.50–3.50 kHz	10.32 ± 4.89	9.95 ± 5.96	0.38	0.71
	3.50–4.50 kHz	12.47 ± 3.07	8.19 ± 4.60	1.09	0.29
	Overall	13.32 ± 8.60	11.09 ± 6.64	0.93	0.36
TOAE reproducibility (%)	0.75–1.25 kHz	79.20 ± 16.48	61.73 ± 10.66	2.58	**0.02***
	1.25–1.75 kHz	89.13 ± 13.53	83.43 ± 22.19	2.47	**0.02***
	1.75–2.50 kHz	88.43 ± 13.10	86.57 ± 15.20	1.67	0.11
	2.50–3.50 kHz	78.23 ± 19.03	70.20 ± 6.40	2.08	**0.03***
	3.50–4.50 kHz	75.30 ± 15.37	61.43 ± 1.25	2.17	**0.02***
	Overall	78.83 ± 14.77	71.83 ± 1.88	1.45	0.16
ABR, LRR	Wave I	1.85 ± 0.10	1.87 ± 0.17	0.70	0.49
	Wave III	3.98 ± 0.23	4.08 ± 0.35	1.57	0.13
	Wave V	5.72 ± 0.18	5.90 ± 0.30	3.19	0.23
	Inter peak I–III	2.10 ± 0.19	2.20 ± 0.37	1.61	0.12
	Inter peak III–V	1.75 ± 0.17	1.84 ± 0.30	1.79	0.09
	Inter peak I–V	3.87 ± 0.21	4.02 ± 0.33	2.85	0.08
ABR (HRR)	Wave V	5.99 ± 0.27	6.16 ± 0.39	2.52	0.08

There were statistically significant differences between the two measures regarding PTA, AR, and TEOAE

Discussion

Although sofosbuvir is Food & Drug Administration (FDA) approved, few studies have been conducted to assess the auditory function in HCV patients treated with this drug, despite the fact that multiple studies reported auditory impairments in previous HCV treatment regimens.

In the current study, the mean age was 41.4 ± 9.9 years with range from 22 to 55 years, with equal affection in both genders. In contrast to our findings, in study of Asal et al. [10], their ages ranged from 20 to 59 years and the majority (60.7%) was more than 40–59 years. This difference may be attributed to larger sample size of their patients (74 patients).

As regards the hearing threshold all participants had bilateral normal peripheral hearing before HCV treatment with combination of sofosbuvir and daclatasvir which is one of our selection criteria.

In the current study in comparison between the results of pre- and post-treatment there was a statistically significant difference in hearing threshold in the right ear at 2 kHz, 4 kHz and 8 kHz, while in the left ear it was highly significance difference at 8 kHz and significant difference at 4 kHz (Tables 2 and 3). In contrast to our findings, in the study of Ismail et al. [11], post-treatment hearing thresholds showed no significant difference from pretreatment evaluation, indicating no hearing affection at these frequencies after treatment.

As regards the results of immitancemetry, there was a statistically significant difference in the ART at 4 kHz in right ear and at 500 HZ and 4 kHz in the left ear in post-treatment results (Tables 2 and 3). This affection can be explained by the ototoxic effect of the combination of sofosbuvir and daclatasvir on the auditory pathway. In contrast to our findings, in the study of Ismail et al. [11] post-treatment results showed no significant difference in ART from pretreatment evaluation; however, they used sofosbuvir in combination with ribavirin rather than daclatasvir in our study.

Regarding TOAE results, we found that there was no statistically significance difference of TOAE S/N in both ears at different frequencies. However, there was a high statistically significance reduction in the reproducibility of 2 TEOAE traces. At 1.75–2.5 kHz ($P < 0.001$), statistically high significance different at 2.5–3.5 kHz ($P < 0.01$), and statistically significance different at 3.5–4.5 kHz ($P < 0.05$) in right ear and in left ear there was a statistically significant difference at each of 0.75–1.25 kHz, 1.25–1.75 kHz, 2.5–3.5 kHz, and 3.5–4.5 kHz ($P < 0.05$). These findings in TEOAs concluded that the combination of sofosbuvir and daclatasvir has a toxic effect on the outer hair cells (OHCs), leading to deterioration of its function. The sensitivity of OAEs as an early indicator of cochlear dysfunction in patients receiving ototoxic agents has been recorded [12, 13]. Some studies have suggested the possibility of early detection of hearing loss by testing otoacoustic emissions (OAE) [14]. Emissions are a strong indication of normal or close to normal cochlear function, and TOAEs are thus an important test of objective assessment. TOAE tests can detect changes in outer hair cell functions before any changes in standard audiometry [15].

The current study showed that ABR pre-treatment findings of all participants were within normal range for the absolute and enters peak latencies in LRR and HRR for both ears, which indicated normal brainstem and auditory nerve response. There was no statistically significant difference in ABR findings for pre- and post-treatment conditions for all participants. This concluded that the combination of treatment have no effect on the auditory nerve and brainstem level.

Conclusion

The combination therapy of daclatasvir and sofosbuvir used in patients with HCV led to deterioration in the hearing threshold in the basic audiological tests (PTA and immitancemetry). Also, it had an adverse effect on the cochlear OHCs which was evidenced by TOAE results. However, this combination has no effect auditory nerve, brain stem functions or in sub-thalamic function (normal ABR at LRR and at HRR).

Recommendations

We recommend performing a routine monitoring of auditory functions in HCV patients treated with daclatasvir and sofosbuvir combination by specialist for early detection of auditory changes to avoid further damage to auditory system. Further studies are needed to evaluate if this hearing loss is reversible or not. Further studies are recommended to evaluate the safety of these drugs on auditory and vestibular systems in a larger group of HCV patients to support our findings, no effect on "short time" to assess this confirmation, we need more time study.

Limits of the study

Duration of study, size sample, and the range age patients.

Abbreviations

HCV: Hepatitis C virus; PTA: Pure tone audiometry; TEOAE: Transient evoked optoacoustic emission; ABR: Auditory brainstem response; RNA: Ribonucleic acid; SRT: Speech reception threshold; WDS: Word discrimination score; PB: Phonetically balanced; SPL: Sound pressure level; ART: Acoustic reflex threshold; SD: Standard deviation; FDA: Food & Drug Administration; LRR: Low repetition rate; HRR: High repetition rate.

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Authors' contributions

SM: Formulate the idea of the research, sharing in writing the research protocol, sharing in writing, editing and; paragraphing the manuscript and publishing the manuscript. EM: Selection of patients, history and examination, sharing in writing, editing and; paragraphing the manuscript and sharing in statistical analysis. ANM: Selection of patients and sharing in writing the manuscript. SM: Writing the research protocol, data collection and sharing in writing the manuscript. UA: Selection of patients and sharing in writing the manuscript. MA: Preparation of the research plan, sharing in writing the research protocol and sharing in writing, editing and; paragraphing the manuscript. The author(s) read and approved the final manuscript.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Ethical approval for conducting the study was granted by the Ethics Committee, Medical College. The work was carried out in accordance with the code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans and was approved by the Ethical Committee of the Faculty of Medicine, Sohag University, Egypt.

Written informed consent was granted by all the participants after explanation of the reasons for conducting the study.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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