Vestibular & Balance Assessment in Hepatitis C Virus Patients Undergoing (Sovaldi/Daklinza) Regimen

Original Article

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ABSTRACT

Background: Previous Hepatitis C Virus (HCV) antiviral drugs reported to cause ototoxicity.
Aim: To detect any possible adverse effects of Sovaldi/ Daklinza regimen related to vestibular & balance functions.
Patients and Methods: Vestibular & balance were assessed in a total number of thirty adult HCV patients , ranging from twenty to sixty years old before administration of (Sovaldi/Daklinza) and three months later , using Vestibular office tests (Head shake test, Head thrust test, Fukuda stepping test& one leg stance). Videonystagmography (VNG), Sensory organization test (SOT) of Dynamic posturagraphy.
Results: After treatment, all patients had normal vestibular office tests, normal VNG testing except for three patients (10% of the study sample) showed positional nystagmus after treatment that wasn't present before receiving Sovaldi/ Daclinza & normal balance function as demonstrated by SOT of Dynamic posturagraphy, with non-statistical significant difference when comparing before and after treatment findings.
Conclusion: Sovaldi/Daklinza regimen used in HCV treatment has no statistically significant effect on vestibular & balance function.

Key Words: Hepatitis C virus, Sovaldi/Daklinza, Vestibular & Balance.

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INTRODUCTION

Hepatitis C virus infection (HCV) is a global health problem, with nearly two millions new infections occurring every year and up to 85% of these becoming chronic infections that pose serious long term health risks[1]

Egypt had the highest known prevalence rate of HCV globally. It was estimated that 14.7 % of the total population were seropositive for HCV[2]

With almost 10 million Egyptians were exposed to the virus and about five to seven millions were in active infection phase. The start of the epidemic in Egypt was attributed to the mass antischistosomiasis treatment campaigns that were conducted in the 1960s and 1970s using insufficiently sterilized intravenous injection equipment[3].

The goal of HCV treatment is to obtain a sustained virologic response (SVR), classically defined as undetectable HCV RNA 12 weeks or more following treatment completion[4].

Different categories of conventional interferon were known as a "key drug" to treat hepatitis C patient[5]. Although, with the addition of ribavirin (RBV), therefore most of the cases remained non-responders or relapsed after the termination, so there was a need to improve the long-term viral clearance rate with more effective and tolerable drug for hepatitis C patients[6].

Several new, all oral, interferon-free regimens became available and more are in development with cure rates consistently over 90% and significantly fewer adverse events compared with previous regimens[7].

Sofosbuvir (Sovaldi®) is a nucleotide analogue of HCV nonstructural protein NS5B inhibiting the virus RNA polymerase of all genotypes[8], used in combination with other Direct Acting Antivirals (DAAs), It should not be administrated as monotherapy since it may lead to drug-resistance[9]. It is used with Daclatasvir (Daklinza®) that inhibits the NS5A protein acts on viral replication, assembly and secretion stages of the viral life cycle. Thereby causing a rapid decline in both intra- and extracellular levels of HCV RNA[10].

Since audiovestibular toxicity has been reported as a consequence of using pegylated and non-pegylated interferons in HCV treatment[11], studying the effect of the

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new widely used Sovaldi in HCV treatment protocols on audiovestibular functions became indispensible.

Ismail[12] reported that sofosbuvir used with ribavirin in chronic hepatitis C had no noticeable effects on cochlear functions. However, to our best knowledge no studies were conducted to evaluate its effect on vestibular functions.

Accordingly, this work was designed to study the effect of sofosbuvir on vestibular and balance functions in patients with chronic hepatitis C.

PATIENTS AND METHODS:

This is a prospective study design that was carried on (30) patients; cases were recruited from the virology unit at Eldemerdash hospital, Ain Shams University over a period of three months.

Subjects:

Thirty adult HCV patients of grade (A) according to child pugh classification[13] for liver disease severity, all of them received (Sofosbuvir 400 mg/Dacltasavir 60 mg) daily for 3 months.

Exclusion Criteria: Patients who had Previous interferon therapy, Decompensated (End stage liver disease), or any associated vestibular complaints before starting the treatment.

Material & Equipment:

1- Tools used for office tests (frenzel glasses for Head Shake test)

2- Computerized four channel Video-nystagmography (VNG) michromedical Tech, meta 4, software version 4.5.

3- Computerized Dynamic Posturography (CPD) Neurocom international, equitest system, software version 8.4.

Methods:

(Every included participant was subjected to the following before & three months after treatment)

Full history taking including HCV history including (onset, course, and duration). Other comorbidities (Diabetes mellitus, Hypertension, etc.……), full description of any positive dizziness complaint after treatment with special emphasis on (Onset, course, frequency, duration and progression of the attacks).character of dizziness (sense of rotation, light headedness, disequilibrium…), accompanying auditory symptoms (ear fullness, tinnitus, hearing loss or ear ache), and if there any associated autonomic symptoms (nausea and/or vomiting).

B) Vestibular assessment:

Vestibular office tests: added to evaluate Vestibulo-Occular Reflex at high frequency range using (Head shake test searching for post head shake nystagmus & Head thrust test at lateral canal plane if there any corrective saccades), and to evaluate Vestibulo-Spinal Reflex using (Fukuda Stepping Test & one leg stance)

(1) Video-Nystagmography (VNG): Classic VNG protocol was performed searching for spontaneous, gaze evoked, positional and positioning nystagmus, bithermal caloric testing. Oculomotor test battery which includes regular random saccade testing, together with smooth pursuit, optokinetic tests.

(2) Sensory Organization Test (SOT) of Computerized Dynamic Post urography (CDP): The Sensory Organization Test (SOT) protocol objectively identifies abnormalities in the patient's use of the three sensory systems that contribute to postural control: somatosensory, visual and vestibular. Posturography testing is an integral part of the assessment of the functional ability and risk of falls.[14]

Statistical methods:

Data Management and Analysis

The collected data was revised, coded, tabulated and introduced to a PC using Statistical package for Social Science (SPSS 20).

Analytical statistics:

1. **Paired t-test** was used to assess the statistical significance of quantitative variable between two means measured twice for the same study group

2. **McNemar test** was used assess the statistical significance of the difference between a qualitative variable measured twice for the same study group

- ***P- value: level of significance:***
  - o *P>0.05*: Non significant (NS).
  - o *P≤ 0.05*: Significant (S).
  - o *P≤0.01*: Highly significant (HS)

RESULTS:

This short term longitudinal study was conducted on 30 adult patients (17 were females, 13 were males) from 20 to 60 years old, the mean age was 42 yrs ± 10.

Most of the study sample) 20 patients, 66.6%) has no significant past history diseases, However anemia was the most common among them (n=4, 13.3%), as anemia of diverse etiology can occur in about 75% in patients with chronic liver disease, due to acute or chronic gastrointestinal hemorrhage, may be as a result of hypersplenism secondary to portal hypertension, or as an associated aplastic anemia[15].

A) Office testing:

Table 1: VOR (head shake and head impulse) before and after treatment:

Test		Before (N=30)		After (N=30)	
		+VE	-VE	+VE	-VE
VOR	Head Shake	0	30	0	30
	Head Thrust	0	30	0	30

Table 2: VSR (fukuda & one leg stance) before and after treatment:

Test		Before (N=30)		After (N=30)	
		+VE	-VE	+VE	-VE
VSR	Fukuda	0	30	0	30
	One leg stance	0	30	0	30

Table 1 & 2 showed normal head shake, head impulse, fukuda & one leg stance tests before and after treatment in all tested patients

B) VNG testing (occulomotor, spontaneous nystagmus, positional, positioning & caloric):

Table 3: Oculomotor tests Gaze evoked nystagmus before and after treatment (GEN):

Test		Before (N=30)		After (N=30)	
		+VE	-VE	+VE	-VE
Oculomotor	Gaze Evoked nystagmus	0	30	0	30

Table 4: Oculomotor tests Optokinetic nystagmus gain before and after treatment(OPK):

Optokinetic nystagmus	Before (Mean ± SD)	After (Mean ± SD)	Paired T test	
			P value	Sig.
Right gain degree	0.86 ± 0.03	0.82 ± 0.02	.096	NS
Left gain degree	0.88 ± 0.03	0.86 ± 0.02	.303	NS

Table 5: Oculomotor tests Saccade test before and after treatment:

Test	Before (Mean ± SD)	After (Mean ± SD)	Paired T test	
Right Saccade Latency(msec)	291.2 ± 9.16	296.27 ± 6.71	.447	NS
Left Saccade Latency(msec)	293.63 ± 10.35	289.5 ± 13.05	.721	NS
Right Saccade accuracy(%)	94.33 ± 1.46	91.7 ± 1.28	.129	NS
Left Saccade accuracy(%)	94.33 ± 0.94	92.67 ± 1.11	.089	NS

Table 6: Oculomotor tests Smooth pursuit gain before and after treatment:

Smooth pursuit (Frequency)	Gain Before (Mean ± SD)	Gain After (Mean ± SD)	Paired T test	
			P value	Sig.
0.1 Hz	0.84 ± 0.02	0.81 ± 0.01	*.227*	NS
0. 2 Hz	0.92 ± 0.02	0.92 ± 0.01	.843	NS
0. 4Hz	0.89 ± 0.02	0.88 ± 0.02	.594	NS
0. 6 Hz	0.72 ± 0.02	0.7 ± 0.02	.302	NS

Table (3-6) did not show any statistically significant difference as regards Gaze evoked nystagmus, OPtokinetic nystagmus (gain), Saccade (accuracy and latency) & smooth pursuit testing before and after treatment.

Table 7: VNG testing Spontaneous nystagmus

Test	Before	After	*P*	Sig.
Spontaneous Nystagmus	-ve	-ve	---	

Table (7) showed that none of the patients had spontaneous nystagmus before treatment neither developed it after treatment.

Table 8: VNG testing (A)Positional nystagmus before & after treatment

Preexisting Positional nystagmus(N)	Before (3)	After (3)	Paired t test	
			P	Sig.
Degree	10 ±2.31	12 ± 1.53	0.51	NS

Table (8-A) showed non-statistical significant difference between the pre- existing nystagmus degree with its degree after treatment.

(B) Criteria of positional nystagmus after treatment

Direction	N	%	Degree (Mean ±SD)	Changing / Fixed direction	Fixation
Up beating	1	3.3%	9	Fixed	Positive
Left/ Right beating	2	6.6%	8.5±1.5	Fixed	Positive

Table (8-B) showed that three patients developed a state of uncompensated peripheral vestibular lesion after treatment.

Table 9: VNG testing Positional nystagmus before and after treatment:

Positional nystagmus		Before(N)		Total	McNemar test	
		Negative	Positive		*p value*	Sig.
After (N)	Negative	24 (80%)	0 (0%)	24 (80%)		
	Positive	3 (10%)	3 (10%)	6 (20%)	0.250	NS
Total		27 (90%)	3 (10%)	30 (100%)		

Table (9) showed non-statistically significant difference between the number of patients with positional nystagmus before and after treatment.

NB There was no positioning nystagmus (Dx hallpike was negative) on both sides in all patients before and after treatment.

Table 10: VNG testing Caloric test

Caloric test		Before	After	Test of sig.	
		Mean ± SD	Mean ± SD	*p value*	sig.
Caloric weakness (% of asymmetry)		9.7 ± 5.25	8.55 ± 3.15	0.184	NS
Fixation index		0.25 ±0.06	0.37±0.05	0.078	NS
Direction preponderance	left	16 (53.33%)	17 (58.62%)	0.774	NS
	right	14 (46.67%)	12 (41.38%)		

Table (10) showed non-statistically significant difference in caloric test results before and after treatment.

Table 11: Sensory organization test (SOT) before & after treatment:

	Before	After	Paired t test	
	Mean ± SD	Mean ± SD	*p value*	sig.
C1	94.68 ± 1.42	94.8 ± 1.28	0.730	NS
C2	92.31 ± 2.07	92.2 ± 2.07	0.786	NS
C3	90.95 ± 3	91.65 ± 1.87	0.146	NS
C4	85.24 ± 7.02	86.89 ± 3.55	0.290	NS
C5	69.28 ± 9.41	71.54 ± 7.41	0.320	NS
C6	64.89 ± 11.73	66.83 ± 7.01	0.226	NS
CS	79.83 ± 4.49	80.83 ± 2.52	0.332	NS

Table (11) showed non-statistical significant difference between before and after treatment SOT results

DISCUSSION

To the best of our knowledge, no studies have been conducted to evaluate the effect of Sovaldi/Daklinza regimen on balance and vestibular function.

Where ***Ismail***[12] found that the therapy with sofosbuvir and ribavirin in chronic hepatitis C had no noticeable effects on cochlear functions

Since Preliminary data by ***Handelsman***[16] showed that the prevalence of auditory and vestibular loss with the use of ototoxic medications is variable where some patients with severe bilateral vestibular loss had normal hearing, while other patients with significant sensorineural hearing loss had normal vestibular system function, this supports the need to include both hearing and vestibular testing in any ototoxic monitoring protocol.

As regards vestibular office tests in this study, all patients were normal before and after treatment, regarding their VOR office tests e.g. (*Head shake test, Head thrust test*) & VSR office tests (*Fukuda Stepping & one leg stance tests*)

Regarding VNG findings: there was no Gaze evoked nystagmus symmetrical optokinetic nystagmus gain, normal saccade test (accuracy, latency and symmetry), normal smooth pursuit gain at all tested frequencies before and after treatment with non-statistical significant difference, thus it may conclude that there is no evident oculomotor affection as a consequence of (Sovaldi/Daklinza) administration.

Although, the patients did not have any vestibular complaints their Pretreatment Positional nystagmus as the only anomaly is non-localizing, it might be attributed to the patients' comorbid factors as hyperlipidemia and/or hypertension, since positional nystagmus has been frequently attributed by clinicians to intermittent vertebrobasilar insufficiency as a result of functional compression or narrowing of vertebral artery e.g. with atheromas from hyperlipidemia or hypertension[17] also, in comparing their pretreatment nystagmus degree, with its degree after treatment it is statistically non-significant.

On the other hand, the results of this study revealed three patients with significant positional nystagmus after treatment that wasn't present before receiving Sovaldi/Daclinza, this reflects uncompensated peripheral vestibular lesion, as a consequence further vestibular assessment is recommended using Video head impulse test (VHIT) for evaluation of other canals at high frequency range , also VEMP to evaluate otolith function .

Regarding Dynamic posturagraphy all patients passed sensory organization test according to the normative data of (CPD Neurocom international, equitest system, software version 8.4) before and after treatment, with non-statistical significant difference between pretreatment and post treatment values excluding affection of balance function as aresult of Sovaldi/Daklinza therapy.

CONCLUSION

There was non-statistical significant affection on balance & vestibular function after sovaldi/Daklinza treatment.

CONFLICT OF INTEREST

There are no conflicts of interest.

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