Balance assessment in Hepatitis C Virus, HCV patients

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Abstract

Background: Previous HCV antiviral drugs reported to cause ototoxicity

Objectives: study the effect of Sovaldi/ Daklinza regimen administration on balance function.

Subjects& Method: Thirty adults HCV patients were assessed, before (Sovaldi/ Daklinza) administration and three months after treatment using Vestibular office tests (Head shake test, Head thrust test, Fukuda steeping test and Modified Clinical Test of Sensory Integration for Balance (mCTSIB), Sensory organization test (SOT) of Dynamic posturagraphy.

Results: After treatment, all patients had normal vestibular office tests, 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 between before and after treatment results.

Conclusions: Sovaldi/ Daklinza regimen used in HCV treatment has no statistically significant effect on vestibular and balance function.

Recommendations: to conduct the study on a larger sample size.

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

تقييم التوازن فى مرضى التهاب الكبدى سى المزمن

المقدمه: تعد الإصابة بفيروس التهاب الكبد الوبائى (سي) عبءا كبيرا على الصحة العامة فى مصر، حيث ان مصر لديها أعلى معدل انتشار للفيروس فى العالم. اقترحت وزارة الصحة المصرية منذ ذلك الحين استراتيجية وطنية جديدة للسيطرة على وباء فيروس التهاب الكبد الوبائى فى مصر من خلال صندوق رأس مال كبير وترويج لسوفوسبوفير Sovaldi كعلاج أولى لها. عرفت فئات مختلفة من الانترفيرون التقليدى باسم "الدواء الرئيسي" لعلاج مرضى التهاب الكبد الوبائي. على الرغم من أن إضافة RBV وتحسين الانترفيرون التقليدى مع التحلل قد عززت معدل الاستجابة الفيروسية المستمرة، ومع ذلك بقيت معظم الحالات غير مستجيبة أو انتكاسة بعد الإنهاء، لذلك كانت هناك حاجة لتحسين التطهير الفيروسى على المدى الطويل معدل مع آثار جانبية اقل وأكثر Sofosbuvir هو تناظر النيوكليوتيدات لبرونتين HC5 غير الإنشائى الذى يحول دون فيروس إنزيم RNA polymerase، بالاقتران مع DAAs الأخرى، لعلاج عدوى HCV لجميع الأنماط الوراثية ٩، فى حين Daclatasvir يمنع NS5A البروتين ويبدو أنه يعمل على التكاثر الفيروسى والتجمع ومراحل إفراز دورة الحياة الفيروسية، مما يؤدى إلى انخفاض سريع فى كل من المستويات داخل وخارج الخلية من HCV RNA، فى الأونة الأخيرة، تمت الموافقة على Daklinza تثبيط التكاثر الفيروسى فى تركيبة مع أدوية أخرى، وخاصة مع Sovaldi.

الهدف: تم تصميم هذه الدراسة الحالية قصيرة الأجل للكشف عن تأثير العلاج المزدوج Sofosbuvir/ Daclatasvir على وظائف الجهاز الدهليزى والتوازن فى ٣٠ مريضا يعانون من التهاب الكبد المزمن سى، تتراوح أعمارهم بين ٢٠– ٦٠ سنة.

المنهجيه: خضع كل مريض لاختبار الجهاز الدهليزى والاتزان باستخدام (اختبارات الاتزان المكتبية، اختبار رأرأة العين بالفيديو وقياس الحركة الديناميكية للجسم بالكمبيوتر) قبل العلاج وبعد ثلاثة أشهر من العلاج وتم الحصول على تاريخ شامل من كل مريض خاصة أى اعراض لها علاقه بعدم الاتزان قبل وبعد العلاج.

النتائج: كان جميع المرضى طبيعيين فيما يتعلق باختبارات الاتزان المكتبية قبل وبعد العلاج. اما ما يتعلق باختبار رأرأة العين بالفيديو، لم يتم اكتشاف أى فرق إحصائى مهم بين المرضى فى مقارنة نتائج ما قبل العلاج بما بعده، ومع ذلك يحتاج ثلاثة مرضى إلى متابعة على المدى الطويل لتقييم ما إذا كانت نتائجهم ستتراجع أو تسوء بمرور الوقت فيما يتعلق بنتائج اما بالنسبه قياس الحركة الديناميكية للجسم بالكمبيوتر، كان لا يوجد اختلاف إحصائى فى مقارنة درجة التوازن لكل حالة قبل وبعد العلاج.

Introduction:

Hepatitis C virus infection (HCV) is a global health problem, with nearly 2 million new infections occurring every year and up to 85% of these becoming chronic infections that pose serious long term health risks.[1]

Egypt has the highest known prevalence rate of HCV globally, with an estimated 14.7% of the total population seropositive for HCV,[2] With almost 10 million Egyptians exposed to the virus and about (5- 7) million active infections.

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, the addition of RBV and improvement of conventional interferon with pegylation had enhanced the rate of sustained virological response, yet 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 less side effects containing drug for hepatitis C patients.[6]

Several new, all oral, interferon- free regimens are available and more are in development. Phase III drug trials of DAA regimens report cure rates consistently over 90% and significantly fewer adverse events compared with previous regimens.[7] However, DAAs should not be administrated as monotherapy because this may lead to drug- resistance.[8]

Sofosbuvir (Sovaldi®) is a nucleotide analogue of HCV nonstructural protein NS5B inhibiting the virus RNA polymerase, in combination with other DAAs, is approved for the treatment of HCV infection of all genotypes,[9] while Daclatasvir (Daklinza®) inhibits the NS5A protein and appears to act on viral replication, assembly and the secretion stages of the viral life cycle, thereby causing a rapid decline in both intra- and extracellular levels of HCV RNA.[10]

Methodology:

This is a prospective study design that was carried on 30 patients from January 2018 to July 2018, cases were recruited from the virology unit at eldemerdash hospital, Ain Shams University over a period of three months.

- Inclusion Criteria: Thirty adult HCV patients of grade (A) according to child pugh classification for liver disease severity between the age of 20 to 60 years old on (Sofosbuvir 400 mg/ Dacltasavir 60 mg) daily for 3 months.
- Exclusion Criteria: Patients who had Previous interferon therapy or Decompensated (End stage liver disease), or any associated vestibular complaints.
- Limitations: Attrition of sample size over time, where there is difficulty in patient's follow up.

Equipments:

1. A double walled sound treated room I. A. C. model 1602.
2. Two channel Audiometer Interacoustics, model AC40, calibrated according to ANSI S. 3.6, 1996, USA
3. Tools used for office tests:
   a. Frenzel glasses for Head Shake and Head Impulse test.
   b. Medium- density foam to conduct mCTSIB.
   c. Stop watch for counting time in mCTSIB test.
4. Computerized Dynamic Posturography (CPD) Neurocom international, equitest system, software version 8.4, USA
5. Audio- vestibular history and examination including otological examination Basic Audiological evaluation (Pure tone audiometry, Speech audiometry& Immitancemetrey) before treatment.
6. Every included participant was subjected to the following before& three months after treatment:
7. Full history taking including Personal history including (age, gender, BMI& any special habits of medical importance). HCV history including (onset, course, duration). Other comorbidities (Diabetes mellitus, Hypertension, etc…), Full description of the dizziness complaint before and after treatment with special emphasis on the: Onset, course, frequency, duration and progression. Character of dizziness (sense of rotation, light headedness, disequilibrium…). Accompanying auditory symptoms (ear fullness, tinnitus, hearing loss and ear ache). Accompanied symptoms (nausea and vomiting).
8. Vestibular Assessment Including: Vestibular office tests: evaluation of Vestibulo- Occular Reflex (Head shake test, Head Thrust Test)& evaluation of Vestibulo- Spinal Reflex (Fukuda Stepping Test& Modified Clinical Test of Sensory Integration for Balance (mCTSIB))
9. 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.[11]

Ethical Considerations:

Informed consent was taken from each cparticipating patient before and after treatment in this study. The study methodology was reviewed and approved by the research review board of the Otorhinolaryngology department, Faculty of medicine, Ain Shams University.

Data Management And Analysis:

The collected data was revised, coded, tabulated and introduced to a PC using Statistical package for Social Science SPSS 20 (IBM, 2015) Data was presented as Descriptive statistics (Mean, Standard deviation (±SD) for numerical data, Frequency& percentage for non- numerical data).

Analytical statistics (Paired t- test was used to assess the statistical significance of the difference between two means measured twice for the same study group) (McNemar test was used assess the statistical significance of the difference between a qualitative variable measured

twice for the same study group) where P≤ 0.05: Significant (S).

Results:

There was nonstatistically significant difference in comparing vestibular test findings before and after treatment.

Table (1) Illustrates Vestibular office tests 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
VSR	Fukuda		0	30	0	30
	mCTSIB	C1	0	30	0	30
		C2	0	30	0	30
		C3	0	30	0	30
		C4	0	30	0	30

(VOR: Vestibulo ocular reflex, VSR: Vestibulospinal reflex, mCTSIB: modified clinical test of sensory integration and balance, C: Condition)

Table (2) Comparison between before& after treatment Sensory organization test (SOT) results

	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(2) showing non- statistical significant difference between before and after treatment SOT results.

Discussion:

There are no generally accepted protocols for monitoring of vestibular function during or following the exposure to potentially ototoxic agents, in part due to the expense associated with laboratory equipment and in part because patients receiving ototoxic medications may be too ill to fully cooperate in vestibular testing, therefore data continues to emerge about test modifications for use as well as assessing the reliability and sensitivity of those various measures.

On account of its excellent performance in clinical trials, Sovaldi drug has got FDA approval on 6 December, 2013 under the breakthrough of therapy designation. This drug is effective against all HCV genotypes, has better safety profile, and low risk of developing resistance. However, careful clinical use and monitoring is still essential, to gather more data on this drug and large post- marketing studies, can solve many unanswered questions for the future of this novel drug.)

The present study aimed to answer the question whether (Sovaldi/ Daclinza) regimen has any vestibular side effects through a comprehensive test battery including (Vestibular office tests, Videonystagmography (VNG) and Dynamic posturagraphy (SOT) before and after treatment. That was carried out on 30 subjects diagnosed with Hepatites C virus (HCV) child pugh classification (A). On (Sofosbuvir 400 mg/Daclatasvir 60 mg) daily for 3 months.

Preliminary data by Handelsman[12] 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 Test& Modified Clinical Test of Sensory Integration for Balance (mCTSIB))

In this study, there were three patients with pretreatment positional nystagmus that might be blamed to their hepatic condition, in line with (13) who found that liver diseases can cause nystagmus, where hepatitis may result in affection of vestibular hair cells. Although, in comparing their pretreatment nystagmus degree, with its degree after treatment it is statistically non- significant

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 where p values equals (0.73, 0.78, 0.14, 0.29, 0.32, 0.22, 0.33 respectively) excluding affection of balance function as aresult of Sovaldi/ Daklinza therapy.

In Conclusion, there was non- statistical significant affection on balance& vestibular function after sovaldi/ Daklinza treatment.

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