Effect of interferon and ribavirin treatment on hearing in chronic hepatitis c patients

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Abstract: Objectives: To study the effect of treatment with interferon and ribavirin on hearing level in chronic hepatitis C virus (HCV) patients. **Patients and Methods:** This study was conducted on 50 patients with compensated chronic HCV. They were selected from hepatology outpatient clinic in Benha university hospital. Audiological assement were done for all patients in audiology clinic, Benha university hospital between March 2010 and March 2012,meanauditory hearing threshold (MHT), day before therapy (MHT-0), after 1st day (MHT-1), after 7th day (MHT-7), after 21st day (MHT-21), monthly during therapy, 1 month after termination of therapy (MHT-30 post TTT) and 2 months after termination of therapy (MHT-60 postTTT). **Results:** There were 30 cases (60%) without noticeable change in audiometry readings & 20 cases (40%) with sensori-neural hearing loss(SNHL), half of them (10 cases) returned totally, (8 cases) of them (16% of total) returned but less than previous and 10% (2 cases) of them (4% of total) disabled. **Conclusion:** Interferon/ribavirin combination therapy may cause SNHL, Possible mechanisms involved include direct ototoxicity, autoimmunity and hematological changes. Hearing loss did not fully resolve after termination of therapy with this combination therapy. So care should be taken for sings of ototoxicity.

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Key Words: Hepatitis C virus, Interferon, Ribavirin, Hearing loss

1. Introduction:

Worldwide, more than 170 million people are infected with hepatitis C virus (HCV), a number that is believed to be an underestimate of the true global prevalence of this disease [(1)].

Interferon-α(INF-α)has been used to treat HCV infection since 1990, with improved outcomes in recent years following the introduction of pegylated interferon (PEG-IFN) and ribavirin (RBV) combination therapy [(2,3).]

PEG-IFN and RBV combination therapy for the treatment of hepatitis C virus (HCV) is well known to be associated with significant adverse effects. Sensori-neural hearing loss (SNHL), that in most cases is unilateral, but may be bilateral has been reported as a consequence of therapy with both pegylated interferon (peg-IFN) and ribavirin but is not a well-known adverse effect. Sudden hearing loss may occur in about 1% of patients on PEG-IFN/ribavirin combination therapy[(4).]

This rate was not different to that observed in an untreated population. Possible mechanisms involved include direct ototoxicity of IFN, autoimmunity, and hematological changes. In contrast to published cases on auditory disability due to standard IFN, hearing loss did not fully resolve after discontinuation of therapy with PEG-IFN. On the other hand, symptoms did hot worsen on continued treatment [(5,6)].

Recently, sudden hearing loss has been reported in patients treated with IFN [(6)]. The reported incidence of hearing loss associated with (IFN-α) ranges from 0.1%to 39.5 **%**[(7,8)]. Interestingly, hearing loss was usually unilateral [(9)]which can make it insidious in onset and difficult to detect. Fortunately, most reported patients recovered after discontinuation of therapy, although some did not recover completely[(10)].

2. Patients and Methods:

This study was conducted on 50 patients whom known to be with compensated chronic HCV. Patients were selected from hepatology outpatient clinic in Benha university hospital, after approval of the relevant ethical committee. The following inclusion criteria was fulfilled: middle aged patients (old age will be excluded to avoid presbyacusis being a cause of hearing loss), a positive test for anti-HCV, HCV RNA by PCR, histological evidence of chronic hepatitis on a liver biopsy taken in the 6months preceding study and absence of contraindications for antiviral therapy. Exclusion criteria were previous history of ear disease, active auditory symptoms at time of treatment, recent alcohol abuse or drug addiction, decompensated liver disease (history of either ascites, bleeding esophageal varices and hepatic encephalopathy), autoimmune disorders and

other sever co- morbidities such as neoplastic, cardiac, hematological and psychiatric diseases.

All patients signed an informed consent prior to the study. The demographic variables of age, sex and educational status were collected before treatment, all patient also interviewed and examined by a qualified ENT physician.

These patients with chronic hepatitis C virus were treated by pegylated interferon (peg-IFN) and ribavirin (RBV) combination therapy. IFN in a dose of 180 ug, subcutaneous, once weekly and (RBV) tablets in a dose of 20 mg/kg with the maximum dose of 1200 mg daily[11,12]. Both are used at least for three months, as the high titer plateau phase, typically last from 60 to 90 days[11].And continuation or disruption was according to the current international standard for HCV RNA.

Hearing evaluation was done in the audiology clinic, Faculty of Medicine, Benha University Hospital.

All patients in this study underwent the following procedures:

Full history taking: personal history, present history of auditory symptoms (hearing loss, tinnitus, vertigo), history to exclude any otological, neuro-otological diseases or other systemic disorders.

Clinical examination: full E.N.T and complete otologic examination to exclude any active auditory symptoms at time of study and general examination to ensure that patient is liable to study and free from any contraindications to treatment.

Basic audiologic evaluation:

(a)Pure tone audiometry (PTA): In the form of air and bone conduction in the frequency range of 250 – 8000 HZ at octave intervals, it was carried out under standardized audiometric conditions. This with inventisSri Audiometer model Bell 11a, 10 (Annex 1x).

(b)Tympanometry: Tympanogram was performed with MAICO, MI24, at the same time with PTA, since IFN can cause flu like symptoms that may interfere with eustachian tube function, also testing of the acoustic reflex threshold for the ipsilateral and the contralateral elicited reflexe.

(c)Transient otoacoustic emissions (TOAEs). It measured using otodynamic analyzer model ILO-96, version 5, day before, after 21days and 60 days after stoppage of treatment [13].This test provides a noninvasive, objective measure of cochlear function. TOAEs were considered present if the whole reproducibility% was≤ 50% according to **kemp, 2002**[14], those who showed an overall reproducibility of 70% were described to have a PASS result.

The Mean Hearing Threshold (MHT): It was determined at seven frequencies from (250 to 8000 Hz) in all patients day before therapy (MHT-0), after 1st day (MHT-1), after 7th day (MHT-7), after 21st day (MHT-21), monthly during IFN therapy, 1 month after the termination of therapy (MHT-30 post TTT) & 2 months after termination of treatment(MHT-60 postTTT).

The collected data underwent statistical analysis.

3. Results:

Our study was done to evaluate the effect of IFN &RBV on hearing. It was carried out on 50 patients with compensated chronic HCV and treated with IFN and RBV.

After full history taking and clinical examination they were investigated with pure tone audiometry, otoacoustic emission (OAE) and tympanometry to evaluate the ototoxic effect of IFN and RBV.

The statistical analysis showed the following results:

Table 1: shows the frequency distribution table for age among studied group

	N=50
Age Range	35.7±2.7 years (31-42) years
30-35 36-40 >40	27 (54%) 20 (40%) 3 (6%)
P	<0.001**

Table 1: shows that the mean average of age in the studied group was 35.7 ranged between 31and42, 54% of studied sample were aged from 30 to35, 40% from 36 to 40 and only 6% more than 40 years old and there is significant difference between numbers of each group.

Table 2: shows the frequency distribution table for sex among studied group

SEX	Male	Female	Total	Z	*P*
	37 (74%	13 (26%)	50 (100%)	23.04	<0.001**

Regarding sex there were 37 males & 13 females (74%) & (26%) respectively and there is significant difference between number of males and females.

Table 3: shows the association between treatment with interferon and OAE results.

	Before day before	During After 2mon.	After 2mo. After	X^2	*P*
Pass	50	30	40	10	
	100%	60%	80%	<0.05*	
Failed	0	20	10	40	
	0%	40%	20%	<0.001*	
Total	50	50	50		
	100%	100%	100%		

Table 3: shows statistically significant difference of OAE before (one day before treatment), during (after 2 months of treatment) and after (2 months after disruption of the treatment) treatment with INF. 20/50 (40%) failed and 30/50 (60%) pass during treatment.

After treatment 10/20 returned to previous state and10/20 failed.

Table 4: shows the association between treatment with interferon and tympanometry results.

			Before	During	After	X^2	*P*
Tympanometry.	A	Count	45	45	41	1.9	NS
	A	%	90.0%	90.0%	82.0%		
	C	Count	5	5	9		
	C	%	10.0%	10.0%	18.0%		
Total		Count	50	50	50		
		%	100.0%	100.0%	100.0%		

Table 4: shows no significant change in tympanometry results during course of treatment with interferon regarding time of administration either before or during or after treatment so there is no association between treatment with interferon and tympanometry results.

Table 5: shows the impacts of treatment course of interferon on audiometry results.

N=50		Mean	±SD	Range
MHT-0	**Right**	**13.6**	**0.7**	**(12 – 14.9)**
	Left	**13.7**	**0.6**	**(12.1 - 14.8)**
MHT-7	**Right**	**15.4**	**2.3**	**(12 - 19)**
	Left	**15.6**	**1.9**	**(12.1 – 20)**
MHT-21	**Right**	**15.8**	**2.8**	**(12 - 25)**
	Left	**15.9**	**2.2**	**(12.1 – 25.5)**
MHT-30	**Right**	**15.9**	**2.9**	**(12 - 25)**
	Left	**16.1**	**2.3**	**(12.1 – 25.8)**
MHT-60	**Right**	**16.2**	**2.2**	**(12 - 26)**
	Left	**16.3**	**2.1**	**(12.1 – 26.2)**
MHT- POST TTT 30	**Right**	**14.2**	**2.4**	**(12 - 18.5)**
	Left	**14.3**	**1.8**	**(12.1 – 18.8)**
MHT-POST TTT 60	**Right**	**14.1**	**2.1**	**(12 – 17.9)**
	Left	**14.2**	**1.5**	**(12.1 – 18)**

There is significant difference between reading of the day before treatment and days 7, 21, 30, 60, 1 month after treatment and 2 months after treatment course finished, also there is a significant difference between reading of day 7 and 1,2 months after treatment course finished but no significant difference between day 7 and days 21,30& 60, and significant difference between reading of day 21 and 1,2 month after treatment course but no significant difference between days 21&30,60. There is no significant difference.Between day 30 and day 60 also there is no significant difference between reading of 1 & 2 months after treatment course and between 1month & 2 months after treatment.

(Table 6): shows the difference between audiometer readings of the right ear in the different time of interferon treatment course

	Paired t	*P*
MHT-0 (PRE) & AHT-7	**-5.3**	**<0.001****
MHT-0 & AHT-21	**-4.93**	**<0.001****
MHT-0 & AHT-30	**-4.82**	**<0.001****
MHT-0 & AHT-60	**-2.86**	**<0.05***
MHT-0 & AHT-30 (POST TTT)	**-2.94**	**<0.05***
MHT-0 & AHT-60 (POST TTT)	**-2.86**	**<0.05***
MHT-7 & AHT-21	**1.3**	**NS**
MHT-7 & AHT-30	**1.5**	**NS**
MHT-7 & AHT-60	**1.6**	**NS**
MHT-7 & AHT-30 (POST TTT)	**2.6**	**<0.05***
MHT-7 & AHT-60 (POST TTT)	**2.8**	**<0.05***
MHT-21 & AHT-60	**1.4**	**NS**
MHT-21 & AHT-30	**1.4**	**NS**
MHT-21 & AHT-60 (POST TTT)	**4.9**	**<0.001****
MHT-30 & AHT-60	**1.6**	**NS**
MHT-30 & AHT-30 (POST TTT)	**2.4**	**<0.05***
MHT-60 & AHT-30 (POST TTT)	**2.6**	**<0.05***
MHT-60 & AHT-60 (POST TTT)	**2.8**	**<0.05***
MHT-30 (POST TTT) & AHT-60 (POST TTT)	**1.1**	**NS**

Table 6 shows that there is a significant difference between reading of before treatment and days 7,21,30,60,1 month after treatment & 2 months after treatment course finished, also there are significant difference between reading of day 7 and 1,2 months after treatment course finished but no significant difference between day 7 and day 21,30& 60, and significant difference between reading of day 21 and 1,2 months after treatment course but no significant difference between days 21&30,60. There is no significant difference between day 30 and day 60. Also there is no significant difference between reading of 1 & 2 months after treatment course and between 1month & 2 months after treatment.

Table 7: shows the difference between audiometer readings of left ear in the different time of interferon treatment course

	Paired t	*P*
MHT-0 (PRE) & AHT-7	**-5.4**	**<0.001****
MHT-0 & AHT-21	**-4.83**	**<0.001****
MHT-0 & AHT-30	**-4.56**	**<0.001****
MHT-0 & AHT-60	**-2.66**	**<0.05***
MHT-0 & AHT-30 (POST TTT)	**-2.64**	**<0.05***
MHT-0 & AHT-60 (POST TTT)	**-2.76**	**<0.05***
MHT-7 & AHT-21	**1.2**	**NS**
MHT-7 & AHT-30	**1.5**	**NS**
MHT-7 & AHT-60	**1.5**	**NS**
MHT-7 & AHT-30 (POST TTT)	**2.6**	**<0.05***
MHT-7 & AHT-60 (POST TTT)	**2.8**	**<0.05***
MHT-21 & AHT-60	**1.4**	**NS**
MHT-21 & AHT-30	**1.3**	**NS**
MHT-21 & AHT-60 (POST TTT)	**4.2**	**<0.001****
MHT-30 & AHT-60	**1.4**	**NS**
MHT-30 & AHT-30 (POST TTT)	**2.3**	**<0.05***
MHT-60 & AHT-30 (POST TTT)	**2.7**	**<0.05***
MHT-60 & AHT-60 (POST TTT)	**2.9**	**<0.05***
MHT-30 (POST TTT) & AHT-60 (POST TTT)	**1.2**	**NS**

Table 7 shows that there is a significant difference between reading of pretreatment and days 7,21,30,60,1 month after treatment & 2 months after treatment course finished, also there are significant difference between reading of day 7 and 1,2 month after treatment course finished but no significant difference between day 7 and day 21,30& 60, and significant difference between reading of day 21 and 1,2 month after treatment course but no significant difference between days 21&30,60. There is no significant difference between day 30 and day 60 also there is no significant difference between reading of 1 & 2 months after treatment course and between 1month & 2 months after treatment.

(Table 8): shows the distribution of cases according to audiometry reading changes and prognosis.

Changed 20 (40%)						Not noticeable Changed 30 (60%)		X^2	*P*
								4	<0.05
Returned totally 10 (50%) (20% from total)		Returned healthy but less than previous 8 (40%) (16% from total)		Disabled 2 (10%) (4% from total)		X^2	*P*		
						26	<0.001		
Unilateral	bilateral	Unilateral	bilateral	unilateral	bilateral				
6 4 left 66.7% 2 right 33.3%	4	6 3 left 50% 3 right 50%	2	2 1 left 50% 1 right 50%	0				
X^2 11		0		0					
P<0.001		NS		NS					

Table 8 shows that there are 30 cases (60%) without noticeable change in audiometry readings and 20 cases (40%) with noticeable change half of them (10 cases) returned totally 6 were unilateral and 4 bilateral, 40% (8 cases)of them returned but less than previous 6 were unilateral and 2 were bilateral and 10% (2 cases) were unilateral disabled.

4. Discussion:

Interferons (IFNs) are cytokines produced by lymphocytes and macrophages whose antiviral, anti-tumoral and immuno-modulatory properties are increasingly exploited for therapeutic purposes. Interferon alpha (IFN-α) has been accepted for use in a wide range as therapy for hepatitis B virus (HBV) hepatitis C virus (HCV) infections. Systemic side effects are common with IFN. In general, neurological side effects involve the central nervous system and develop after long-term and high-dose drug use. PEG-interferon and ribavirin combination therapy for the treatment of hepatitis C virus (HCV) is well known to be associated with significant adverse effects such as flu-like syndrome, anosmia, hematological, infectious, cardiovascular, renal, autoimmune, and psychiatric problems, auditory complaints due to IFN alpha administration are rare [(15).]

Development of SNHL due to direct ototoxicity of combination therapy is unlikely, while it may be hypothesized that autoimmunity precipitated or probably exacerbated by INF therapy is a possible mechanism in pathogenesis of microvascular damage of the inner ear and the finding of autoantibodies against the endothelial cells supported our hypothesis[(8).]

The sensitivity of OAEs to early identification of cochlear damage in patients receiving ototoxic agent has been reported. This decrease in The OAEs amplitude is considered as an early sign of an ototoxic secondary effect, probably due to outer hearing cells (OHCs) damage [(16,17).]

SNHL, that in most cases is unilateral, has been reported as a consequence of therapy with both pegylated interferon (PEG-INF) and ribavirin but is not a well-known adverse effect [(2,3,6).]

In our study we determined the mean hearing thresholds (MHT) at seven frequencies from (250 to 8000 Hz) in all patients day before therapy (MHT-0), after 7th day (MHT-7), after 21st day (MHT-21), monthly during IFN therapy, 1 month (MHT-30 post TTT) and 2 months (MHT-60 post TTT) after the termination of therapy.

Hearing loss defined as an elevation over baseline threshold of >10dB for all frequencies or more than 20dB for any individual frequency [(18).]

Hearing loss occurred early at the 7th day of starting treatment and increase until the 21st day, it continued to increase during IFN therapy.

Regarding the audiometry there were significant difference between audiometer reading

of the day before treatment and day 7, 21, 30, 60, 1 month after treatment and 2 months after treatment course finished, also there were significant difference between reading of day 7 and day 60 & 1,2months after treatment course finished, but no significant difference between reading of day 7 and day 21 & 30 and significant difference between reading of day 21and day 60&1, 2months after treatment course but no significant difference between day 21& 30. There was significant difference between day 30 and day 60, 1month after treatment also there was no significant difference between reading of day 60 & 1, 2months after treatment course and between 1momth &2months after treatment. And this in agreement with **Forman *et al.*, 2004, Akyol MU *et al.*, 2001 and Candoni *et al.*,.1998**[5,18,19]. In this study there were 30 cases (60%) without noticeable change in audiometry readings and 20 cases (40%) with SNHL, half of them (10 cases) returned totally, (8 cases) of them (16% of total) returned but less than previous levels and 10% (2cases) of them (4% of total)disabled. In our result the auditory disability developed in early stages. Our results were in accordance with most of the authors but not in accordance with **Gorur *et al.*, 2003**[20], about the full recovery for all cases as he reported that INF alpha administration in patients with hepatitis c may cause mild reversible hearing loss (hearing loss completely recovered one month after the cessation of the INF alpha).

In this study according to OAE that was done before, during and after treatment course we found that 20/50 failed and 30/50 pass during treatment. After cessation of treatment there were 10/20 returned to previous state and 10/20 failed. And this in agreement with **Forman *et al.*,2004**[5], who reported that inner ear affection not improved completely after cessation of treatment.

Conclusion:

Dual therapy with Interferon and Ribavirin in Hepatitis C Virus patients could cause damage to cochlea leading to SNHL. Hearing loss is usually unilateral but may be bilateral. It occurs as early as 7days of treatment but may occur lately.

- They could cause OHCs damage which was reflected on OAE, also could cause inner hair cells which was reflected on audiometry as cochlear SNHL in some cases.
- Hearing loss may occur gradually but there is a possibility of sudden occurrence.
- Hearing loss is usually reversible but in some cases may not return to normal.

Recommendation:

By the end of this study, we should know that hearing loss may occur to HCV patients treated with IFN and Ribavirin, so we recommend that these patients should be informed by this possibility.

We recommend that HCV patients receiving dual therapy with INF and Ribavirin, must have audilogical assessment by pure tone audiometry, tympanometry and OAEs before, during and after treatment as well as a long term follow up should done for early detection of ototoxicity. Also if any complain of hearing loss either (sudden or gradual) or tinnitus during the dual therapy, treatment should be withdrawn and an autoimmune-microvascular pathogenesis should be excluded.

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