Original Article

Frequency of Thyroid Dysfunction in Patients of Chronic Hepatitis C Treated with Interferon Alpha 2B and Ribavirin

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Objective: To determine the frequency of thyroid dysfunction in patients of chronic hepatitis C treated with Interferon alpha 2b and Ribavirin.

Methods: A total of 120 cases having active hepatitis C assessed by HCV RNA PCR as per operational definition for atleast 3 months between 15 years to 60 years of both gender were included in the study from outdoor of Services Hospital Lahore after a written informed consent. All the demographics including name, age, gender and address were entered in a pre-defined questionnaire. Patients were treated with Interferon alpha 2b (dose) three million international units subcutaneously three times a week and Ribavirin (dose) 1200 mg oral daily for 24 weeks. As per hospital routine Thyroid dysfunction was evaluated as per operational definitions by collecting 4ml of blood in a 5cc syringe at 0 (baseline) and 12 week. Presence or absence of thyroid dysfunction at 12 weeks was labelled as per operational definition.

Results: In our study, out of 120 cases, 42.5%(n=51) were between 15-40 years while 57.5% (n=69) were between 41-60 years of age, mean±sd was calculated as 42.49±11.54 years, 59.17% (n=71) were male while 40.83% (n=49) were females, frequency of thyroid dysfunction in patients of chronic hepatitis C treated with interferon alpha 2b and ribavirin was recorded in 21.67% (n=26).

Conclusion: We concluded that the frequency of thyroid dysfunction in patients of chronic hepatitis C treated with Interferon alpha 2b and Ribavirin is not very high but reaches at a considerable level and necessary steps should be taken for the management of this morbidity while interferon therapy is given to the Hepatitis C virus cases.

Keywords: Chronic hepatitis C, treatment, interferon alpha 2b and ribavirin, thyroid dysfunction.

Introduction

Globally, the hepatitis C virus (HCV) has infected an estimated 170 million people, most of whom are chronically infected with a high risk of cirrhosis and hepatocellular carcinoma and they serve as a reservoir for transmission to others.[1] Interferon-alpha (IFN-α) based antivirus therapy, regular IFN-α or pegylated Interferon alpha in combination with Ribavirin, is recognized as being a highly effective treatment for patients with chronic hepatitis C (CHC).This therapy results in a sustained virological response (SVR) in 4050% of patients with genotype 1, and around 80% in those infected with genotype 2 and 3.[2]

Despite their favourable efficacy, these IFN-α based regimens are also accompanied by many well-known adverse effects, including; fever, depression, anemia, neutropenia, thrombocytopenia and endocrine side effects.[3] The most commonly documented extra hepatic endocrine side effect of these IFN-α based regimens is the production of auto antibodies and the development of thyroid dysfunction (TD).

Retrospective analysis of 109 HCV-treated patients (for 6 to 12 months, according to HCV genotype) for the period 1996 to 2008. Thyroid function tests were performed every 3 months during therapy and after discontinuation (3 months to 12 years). Routine laboratory tests and virological assessment were performed according to generally accepted practice. TD was observed in 26 patients (23.85%) who were treated with Interferon alpha-2b (3 million international unit) subcutaneously three times a week and Ribavirin oral 1200mg daily.[4]

One hundred cases of CHC, proven by anti-HCV and HCV RNA-positive with baseline TSH, FT4 and FT3 within the normal reference range, who were treated with interferon alpha-2b (3 million international unit subcutaneously three times per week) and oral ribavirin (1000-1200 mg per day) were included in this study. All patients were assessed for TSH, FT4, FT3 levels at 12 weeks and 24 weeks during therapy. Among the 100 patie ts, overt thyroid disease developed in13 (13%) and sub-clinical thyroid disease

in 5 (5%). Out of 13 patients of overt thyroid disorders, 11 (84.6%) had hypothyroidism and 02 (15.3%) hyperthyroidism. Four (80%) patients were of sub-clinical hypothyroidism and 01 (20%) patient was of sub-clinical hyperthyroidism. Overall, thyroid disorders developed in 18 (18%) both as overt and sub-clinical thyroid disorders.[5] In another study in which both drugs were given to a single patients thyroid dysfunction (TSH <0.1 or >5 mU/L) had developed in 58 patients (12.6%).[9]

One hundred and sixty seven non-cirrhotic chronic hepatitis C patients were grouped into treatment group (n=107) and control group (n=60) awaiting treatment. Baseline serum (s) Alanine Transferase (ALT) and S. Aspartate Transferase (AST) were measured by IFCC method. Serum Thyroid Stimulating Hormone (S. TSH), serum free thyroxine (S. Free T4) and serum total triiodothyronine (S.T3) level were determined by chemiluminescence. Study group patients underwent 24 weeks Interferon and Ribavirin therapy and were followed-up for thyroid dysfunction at weeks 0, 12 and 24. Control group patients underwent the same tests at weeks 0, 12 and 24. Out of 107 patients of treatment group, 20 patients (18.69%) developed thyroid dysfunction whereas only one patient developed TD in control group out of 60 patients.[6]

The rationale of this study is to determine the actual frequency of thyroid dysfunction in patients using Interferon and Ribavarin. There are controversial results in the literature[6,7] so this study will clarify the results. Moreover there was no local study available on effect of interferon on thyroid function and ethnicity also has impact on frequency as stated by Mameen JS[8] so this will reveal us weather we have to consider TD in our population before advising these medications in patients of Chronic Hepatitis C.

Methods

Study was conducted in Medical unit M-IV Services Hospital, Lahore. It is descriptive case series.

The sample size estimated is 120 using 95% confidence level with 7% margin of error with an expected percentage of thyroid dysfunction as 18%.Ptients of both genders between 15 years to 60 years and patients having active hepatitis C assessed by HCV RNA PCR as per operational definition for atleast 3 months. Patients who had any type of throat surgery. e.g Thyroidectomy Patients or with thyroid abnormality before onset of treatment.e.g Hyperthyroidism or Hypothyroidism as per operational definition and Patients with diabetes mellitus (Previous medical recoror who had taken treatment for Hepatitis C were excluded.

After fulfilling inclusion and exclusion criteria a total of 120 patiets presenting in outdoor of Services Hospital Lahore who have chronic hepatitis C as per operational definition were enrolled in this study after a written informed consent. All the demographics including name, age, gender and address were entered in a pre-defined questionnaire. Patients were treated with Interferon alpha 2b (dose) three million international units subcutaneously three times a week and Ribavirin (dose) 1200 mg oral daily for 24 weeks. As per hospital routine Thyroid dysfunction was evaluated as per operational definitions by collecting 4ml of blood in a 5cc syringe at 0 (baseline) and 12 week. Presence or absence of thyroid dysfunction at 12 weeks was labelled as per operational definition.

Data was entered on computer software SPSS version 17. Quantitative data like age, TSH and T3 levels were presented by mean and standard deviation while qualitative data like gender and thyroid dysfunction was presented by frequency and percentages. Data was stratified for age, gender, duration of Hepatitis C to deal with effect modifiers. Poststratification Chi-square test was applied. P-value ≤0.05 was considered significant.

Results

A total of 120 cases fulfilling the inclusion/exclusion criteria were enrolled to determine the frequency of thyroid dysfunction in patients of chronic hepatitis C treated with Interferon alpha 2b and Ribavirin. Age distribution of the patients was done showing that 42.5%(n=51) were between 15-40 years while 57.5%(n=69) were between 41-60 years of age, mean+sd was calculated as 42.49±11.54 years. **(Table1)** Patients were distributed according to gender showing that 59.17%(n=71) were male while 40.83%(n=49) were females. **(Table-2**) Mean TSH and T3 levels were calculated as 3.29±2.44 and 144.98±49.45.

(Table-3) Frequency of thyroid dysfunction in patients of chronic hepatitis C treated with interferon alpha 2b and ribavirin was recorded in 21.67%(n=26) while 78.33%(n=94) had no findings of the morbidity. **(Table-4)** Stratification for frequency of thyroid dysfunction in patients of chronic hepatitis C treated with interferon alpha 2b and ribavirin age, gender and duration of hepatitis C virus were recorded and presented in **(Table- 5,6,7)**

Table-1: Age distribution (n=120).

Age (in years)	No of Patients	Percentage
15-40	51	42.5
41-60	69	57.5
120	120	100
Total	Coma	3
Mean±sd	42.49±11.54	

Table-2: Sex distribution (n=120).

Age (in years)	No of Patients	Percentage
Male	71	59.17
Female	49	40.83
Total	120	100

Table-3: Mean TSH and T3 Levels (n=120).

TSH/T3	Mean	Percentage
TSH	3.29	2.44
T3	144.98	49.45

Table-4: Frequency of thyroid dysfunction in patients of chronic hepatitis c treated with interferon alpha 2b and ribavirin (n=120).

Thyroid dysfunction	No. Of Patients	Percentage
Yes	26	21.67
No	9	78.33
Total	120	100

Table-5: Stratification for frequency of thyroid dysfunction with regards to age.

In Years	Thyroid dysfunction (N=26)		P-value
	Yes	No	
15-40	08	43	0.17
41-60	18	51	

Table-6: Stratification for frequency of thyroid dysfunction with regards to gender.

Gender	Thyroid dysfunction (N=26)		P-value
	Yes	No	
Male	15	56	0.86
Female	11	38	

Table-7: Stratification for frequency of thyroid dysfunction with regards to duration of hepatitis c.

Duration of hepatitis C	Thyroid dysfunction (N=26)		P-value
	Yes	No	
1-3 Years	12	42	0.86
>3 years	14	52	

Discussion

Hepatitis-C virus infection is a worldwide problem and its natural, unfavorable course is still a challenge for the hepatologist. The standard of treatment is combined therapy with interferon-alpha and ribavirin. Treatment of hepatitis-C infection often results in many endocrinological disturbances of which thyroid dysfunction is most prevalent1. Interferons are a family of naturally occurring, small protein molecules with molecular weight of 15,000-20,000 Da. They are included in three groups, IFN alfa, IFN-beta, IFN-gamma with different biological effects and variable duration of activity. Ribavirin is a synthetic Guanoside nucleoside analogue that exerts immuno modulatory effects by inducing cytokines in the against HCV infection and is frequently given with IFN in the treatment of chronic hepatitis C patients. A high prevalence of thyroid gland dysfunction has been reported in hepatitis C virus (HCV) infected patients before and after interferon Alfa therapy and some data also show a high prevalence of anti-HCV antibody in patients with autoimmune thyroiditis.

We planned this study with the view to determine the actual frequency of thyroid dysfunction in patients using Interferon and Ribavarin due to the fact that there are controversial results in the literature[6,7] so this study may clarify the results.

In our study, out of 120 cases, 42.5%(n=51) were between 15-40 years while 57.5%(n=69) were between 41-60 years of age, mean±sd was calculated as 42.49±11.54 years, 59.17%(n=71) were male while 40.83%(n=49) were females, frequency of thyroid dysfunction in patients of chronic hepatitis C treated with interferon alpha 2b and ribavirin was recorded in 21.67%(n=26).

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ribavirin (1000-1200 mg per day) were included in this study. All patients were assessed for TSH, FT4, FT3 levels at 12 weeks and 24 weeks during therapy. Among the 100 patients, overt thyroid disease developed in 13 (13%) and sub-clinical thyroid disease in 5 (5%). Out of 13 patients of overt thyroid disorders, 11 (84.6%) had hypothyroidism and 02 (15.3%) hyperthyroidism. Four (80%) patients were of sub-clinical hypothyroidism and 01 (20%) patient was of sub-clinical hyperthyroidism. Overall, thyroid disorders developed in 18 (18%) both as overt and sub-clinical thyroid disorders.[5] In another study in which both drugs were given to a single patients thyroid dysfunction (TSH <0.1 or >5 mU/L) had developed in 58 patients (12.6%).[9] these findings are significantly lower than our study, we could not identify any reason for this difference.

One hundred and sixty seven non-cirrhotic chronic hepatitis C patients were grouped into treatment group (n=107) and control group (n=60) awaiting treatment. Baseline serum (s) Alanine Transferase (ALT) and S. Aspartate Transferase (AST) were measured by IFCC method. Serum Thyroid Stimulating Hormone (S. TSH), serum free thyroxine (S. Free T4) and serum total triiodothyronine (S.T3) level were determined by chemiluminescence. Study group patients underwent 24 weeks Interferon and Ribavirin therapy and were followed-up for thyroid dysfunction at weeks 0, 12 and 24. Control group patients underwent the same tests at weeks 0, 12 and 24. Out of 107 patients of treatment group, 20 patients (18.69%) developed thyroid dysfunction whereas only one patient developed TD in control group out of 60 patients.[6] These findings support our results.

However, the findings of our study may be among the primary data in our population and some other studies may be done to determine this frequency in other parts of our country.

Conclusion

We concluded that the frequency of thyroid dysfunction in patients of chronic hepatitis C treated with Interferon alpha 2b and Ribavirin is not very high but reaches at a considerable level and necessary steps should be taken for the management of this morbidity while interferon therapy is given to the Hepatitis C virus cases.

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References

1. Negro F, Alberti A. The global health burden of hepatitis C virus infection. Liver Int. 2011;31(Suppl 2):1-3.
2. McHutchison JG, Lawitz EJ, Shiffman ML, Muir AJ, Galler GW, Mc-Cone J. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. N Engl J Med. 2009;361(6):580-93.
3. Sokal EM, Bourgois A, Stephenne X, Silveira T, Porta G, Gardovska D]. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection in children and adolescents. J Hepatol. 2010;52 (6):827-31.
4. Vasiliadis T, Anagnostis P, Nalmpantidis G, Soufleris K, Patsiaoura K, Grammatikos N. Thyroid dysfunction and long-term outcome during and after interferon-alpha therapy in patients with chronic hepatitis C. Ann Acad Med Singapore. 2011;40(9):394-400.
5. Masood N, Ghori R, Memon A, Memon S, Memon KI, Memon I. Frequency of Thyroid Disorders During Interferon and Ribavirin Therapy in Chronic Hepatitis C Inf- ection. JCPSP 2008;18(6):347-51.
6. Nadeem A, Aslam M, Khan DA, Tassawar Hussain T, Khan SA. Effects of Combined Interferon Alpha and Ribavirin Therapy on Thyroid Functions in Patients with Chronic Hepatitis C. JCPSP 2009;19 (2): 86-89.
7. Andrade LJ, Atta AM, Atta ML, Mangabeira CN, Paraná R. Thyroid disorders in patients with chronic hepatitis C using interferon-alpha and ribavirin therapy. Braz J Infect Dis. 2011;15(4):377-81.
8. Mammen JS, Ghazarian SR, Rosen A, Ladenson PW. Patterns of interferon-alpha-induced thyroid dysfunction vary with ethnicity, sex, smoking status, and pre-treatment thyrotropin in an international cohort of patients treated for hepatitis C. Thyroid. 2013;23(9):1151-8.
9. Kee KM, Lee CM, Wang JH, Tung HD, Changchien CS, Lu SN, Wang PW. Thyroid dysfunction in patients with chronic hepatitis C receiving a combined therapy of interferon and ribavirin: incidence, associated factors and prognosis. J Gastroenterol Hepatol. 2006 Jan;21(1 Pt 2):319-26.