MEAN HAMILTON RATING SCALE FOR DEPRESSION USING PEGYLATED INTERFERON PLUS RIBAVARIN THERAPY FOR CHRONIC HEPATITIS C

Amjad Ali, Ahmad Nawaz Babar, M. Amin Khan

Department of Medicine, Bacha Khan Medical College, Mardan - Pakistan

ABSTRACT

Objective: To compare mean depression scores on Hamilton rating scale before and after pegylated interferon therapy for chronic hepatitis C.

Material and Methods: This study was conduced in the department of medicine Mardan Medical Complex, Mardan from July 2013 to January 2014. It was a Quasi-Experimental Study, patients suffering from chronic hepatitis C as confirmed by HCV anti bodies by ELISA and Positive Quantitative PCR and those who required treatment with pegylated interferon plus ribavarin were included in the study. After getting ethical approval and informed consent, patients were interviewed to measure the base line depression by presenting the Hamilton Rating Scale for depression (HAM-D) (Urdu version). All patients were followed and interviewed again at 12th week (HAM-D) to measure the score. Paired T-test was used to compare the difference in the depression score before and after treatment.

Results: The study population consisted of 87 patients with mean age of 36.41 years ± 8.282 SD. There were 49 (56.3%) male and 38 (43.7%) female patients. The baseline depression score ranged from 1.0 to 16.0 with mean score of 4.50 ± 2.761 SD. 11.5% patients (10 out of 87) were having mild depression (HAM-D score, 7-17) before starting treatment. The depression score at the end of treatment ranged from 3.0 to 29.0 with mean depression score of 8.33 ± 5.455 SD. 31/87 (35.6%) patients had depression based on HAM-D. The baseline mean depression score using Hamilton Depression Rating Scale was 4.50 ± 2.761 SD which rose to 8.33 ± 5.455 SD after 12 weeks. The mean difference in depression score was 3.82 ± 4.786 SD and this difference was statistically significant.

Conclusion: Depression is a relatively common complication of treatment with pegylated interferon plus ribavarin for chronic hepatitis C infection.

Key Words: Pegylated Interferons, Hepatitis C, Depression, Hamilton scale, Ribavarin.

INTRODUCTION

Hepatitis C is the most common cause of chronic liver disease and 20 to 30% of patients develop cirrhosis of liver with a risk of hepatocellular carcinoma. The standard of care antiviral therapy recommended to treat hepatitis C virus infection is with pegylated interferon in combination with ribavarin. Combination antiviral therapy can lead to major depression in more than one third patients which compromise treatment compliance and frequently lead to premature discontinuation of antiviral therapy. Depression can be encountered or aggravated during interferon and ribavarin treatment for chronic hepatitis C. Hepatitis C virus affects about 180 million people globally (about 3% of the world's population) and is one of the major causes of chronic liver disease.[1] Among patients infected chronically with hepatitis C 10-20% progress to cirrhosis of liver on average over the period of 20 years.[2] In general population of Pakistan the prevalence of chronic hepatitis C patients is 4.7% and it is much more higher in high risk groups.[3] The standard of care antiviral therapy recommended to treat hepatitis C virus infection is with pegylated interferon (PEG-INF) in combination with ribavarin (RBV).[4] The primary objective of this therapy is to obtained a virological response and to decrease the disease progression and hepatic disease related mortality.[5]

The combination therapy for chronic hepatitis C (CHC) has its own side effects the most common of which are fatigue, flu like symptoms, anemia, leucopenia and thrombocytopenia. Besides that in one study the combination therapy with Interferon and RBV leads to major depression in percentage of about 37% which compromise treatment compliance and frequently leads to premature discontinuation of antiviral therapy[6]. Inci-

Address for Correspondence:
Dr. Amjad Ali
Associate Professor
Department of Medicine, BKMC, Mardan - Pakistan
Cell: 0333-9418546
Email: dramjadali75@gmail.com

dent rates of depression are high in the first 4 to 8 weeks and prevalence increases during the first 6 months of treatment[8,9].

The study is designed to compare the mean depression scores before and after treatment with PEG-INF and RBV for chronic hepatitis C. This study will provide us with local hard evidence of changes in depression scores after interferon therapy.

MATERIAL AND METHODS

This was a Quasi-Experimental Study, conducted in the department of medicine, Mardan Medical Complex, Mardan, from July 2013 to January 2014. All adult patients from either gender suffering from CHC as confirmed by HCV anti bodies by ELISA and positive Quantitative PCR fulfilling the criteria for combination therapy with PEG-INF and RBV in fixed dose combination, were enrolled in the study. The patients already diagnosed as depressed, having co-infection with hepatitis B or human immunodeficiency virus or having cirrhosis of liver were excluded from the study.

Chronic hepatitis C was defined as hepatitis C virus infection which lasts longer than six months and was labeled when HCV antibody was positive tested by 3rd generation ELISA and HCV RNA positive by PCR (>50IU/ml) measured in the laboratory. Depression was diagnosed and quantified by applying the Hamilton Rating Scale for Depression (HAM-D) which consists of questions 21 variables. Depression was evaluated by 3-5 possible responses which increase in severity. The cut off score was 6 which means HAM-D score 7 or above was labeled as depressed at 12 weeks follow up.

After approval from ethical committee data was collected from all the CHC patients before starting the combination of PEG-INF and RBV were interviewed properly to measure the base line depression by presenting the structured questionnaire of Hamilton Rating Scale for depression (Urdu version). Demographic details were recorded on predesigned proforma. All the patients who were put on combination of antiviral therapy were followed and interviewed at 12th week by applying HAM-D questionnaire again to measure the score. All the interviews for measuring HAM-D score were conducted in the presence of a consultant psychiatrist fellow of CPSP.

The data were entered and analyzed using SPSS version 19.0. Quantitative variables like age, HAM-D score before and HAM-D score after treatment were described in terms of mean ± standard deviation. Categorical variables like gender were presented as frequencies and percentages. Paired T-test was used to compare the difference in the HAM-D score before and after treatment. Mean Change in HAM-D score was stratified among age and gender to see the effect modifications.

RESULTS

The study population consisted of 87 patients. Age of the study population ranged from 18 to 50 years with mean age of 36.41 ± 8.282 SD. Most patients were more than 40 years old. There were 49 (56.3%) male and 38 (43.7%) female patients with male to female ratio of 1.2:1. Most of the patients were of genotype 3 (73.56%). Different characteristics of the survey is shown in Table 1.

The base line depression score ranged from 1.0 to 16.0 with mean score of 4.50 ± 2.761 SD. Although we excluded those patients who were already diagnosed with depression, 11.5% patients were having mild depression (HAM-D score, 7-17) when they were screened with HAM-D questionnaire. The depression score at the 12th week of treatment ranged from 3.0 to 29.0 with mean depression score of 8.33 ± 5.455 SD. Fifty-six out of 87 patients (64.4%) had no depression (depression score < 6) while 31 (35.6%) patients had depression based on HAM-D. However most patients had mild depression (depression score 7-17) and only

Table 1: Characteristics of the Sample before starting antiviral therapy

Characteristics	Study Population (n=87)
Age (Y) mean ± SD	36.41 ± 8.28
Gender	
Male	49 (56.3%)
Female	38 (43.7%)
HCV Genotype	
Genotype 1	18 (20.68%)
Genotype 2	5 (5.74%)
Genotype 3	64 (73.56%)
Serum Analysis Mean ± SD ALT U/L	86.4 ± 60.9
Hemoglobin g/dl	14.1±1.6
Neutrophil count x 10^3 /μl	4.2 ± 1.2
Platelet count x 10^3/ μl	211.5 ± 54.1
HADS-depression Score	4.50±2.761 SD

Table 2: Comparison of the Difference in the HAM-D Scores among different age

Age Groups	Statistics	Baseline score	Score at the end
20-30 years	No. of patients	26	26
	Minimum	2.00	3.00
	Maximum	12.00	22.00
	Mean	4.5769	7.5385
	Std. Deviation	2.13866	4.78523
31-40 years	No. of patients	30	30
	Minimum	1.00	4.00
	Maximum	12.00	23.00
	Mean	4.2000	8.9667
	Std. Deviation	2.17192	5.59238
>40 years	No. of patients	31	31
	Minimum	2.00	4.00
	Maximum	16.00	29.00
	Mean	4.7419	8.3871
	Std. Deviation	3.65119	5.91990
P value	Effect of age	0.74	0.62

one patient developed severe depression at 12th weeks follow up (depression score >24).

Paired t-test was used to compare the difference in the HAM-D score before and after treatment. In our study the baseline mean depression score using Hamilton Depression Rating Scale was 4.50 ± 2.761 SD which rose to 8.33 ± 5.455 SD after 12 weeks. The mean difference in depression score was 3.82 ± 4.786 SD and this difference was statistically significant. Since the significance value for change in depression is less than 0.05, so we can conclude that the average increase in depression score of 3.82 ± 4.786 SD is not due to chance variation, and can be attributed to the combination of interferon and ribavirin therapy.

Mean Change in HAM-D scores was also stratified among different age groups and gender to see the effect modifications. The effect of both the age and gender on the mean change in HAM-D scores before and after treatment was statistically not significant with p value of more than 0.05 as shown in Table 2.

DISCUSSION

Chronic hepatitis C is one of the major health problems in Pakistan, with prevalence as high as 16% in certain areas.[10] Standard pharmacologic treatment for chronic hepatitis C virus (HCV) infection is the antiviral combination of PEG-IFN and RBV. However interferon treatment is associated with psychiatric adverse effects such as depression, mania, psychosis and suicidal tendencies.[11,12] Depression is more common in the first 4 to 8 weeks and prevalence increases during the first 6 months of treatment. Our results showed significant level of depressive symptoms in persons with CHC before interferon therapy (11%). This finding is similar to other international studies that reported depression in 10 to 40% patients with CHC.[13,14] According to Lee CH et al. every fourth person with hepatitis C had depressive symptoms and about 60% of them required psychiatric treatment.[15] The reasons for such high rate of depression in CHC patients before treatment could be explained by either-biological factors (neurotoxicity of HCV and numerous changes in the cerebral metabolism) or psycho-social factors (reaction to unfavourable CHC prognosis, negative expectation of the outcome, insufficient information about the disease and stigmatization, etc).[16,17] In one study baseline depression score using Hamilton Depression Rating Scale was 5.6 ± 4.7SD which rose to 8.4 ± 5SD after 12 weeks.[8] A study presents a case series of 11 patients who developed severe depression with suicidal attempts or ideation that had no previous history of depression.[9] The patients usually are not screened for depression before starting the antiviral therapy and during the follow up.

We found an increase in overall HAM-D scores on follow-up visits at the 12th week of interferon therapy. After 12 weeks, 36% of the patients had depressive symptoms: although the majority had mild depression (27.6%), moderate and severe intensity of depression was found in about 8% of our sample. There are other studies where incidence of interferon induced depression in patients with hepatitis C was identified in significantly lower percentage. For example Davis GL et al. found depression in 16%, and Pariante et al. found unspecified depressive disorder in 6%.[18,19] Moreover, some studies do not confirmed the association between interferon therapy and depression in CHC. Davis did not found any difference in the rate of depression between the patients treated with interferon alpha and placebo group, and Mulder et al. showed that interferon treatment is not associated with neither onset nor worsening of psychiatric symptoms in patients with hepatitis C.[20, 21] These differences could be due to differences in criteria, treatment protocol and cutoff values used for depression.

In our study we screened patients for depression before and only once at 12th week of treatment. This methodology is based on the fact that the peak of depressive symptoms are evident at 12th week in most patients as majority of the studies have shown that the onset of depression on interferon was around 12 weeks of therapy. Martin-Santoz et al, presented a prospective cohort of patients with CHC and they found that in more than 90% of the subjects with depression on interferon, depressive symptoms appeared during the first 12 weeks.[22] Similarly Bonaccorso et al, using the DSM-IV criteria and the Montgomery Asberg Depression Rating Scale reported that 40.7% were clinically depressive after 3 month of treatment.[23] However, Fontana et al has reported that the onset of depressive symptoms might be evident in the later stages i.e. 24-48 weeks.[24]

Certain risk factors contribute to the appearance of depressive symptoms in CHC patients who are on interferon therapy. The most common associations are reported for gender, age, lifetime depression and/or suicidal tendency and duration of illness. However our study showed that gender and age had no significant effect on depression scores. Some studies pointed out sex differences in the incidence of depression in this population. Nesic et al. found that females had more psychiatric side effects when on interferon therapy.[25] In contrary, Bonaccorso et al. and Martin-Santoz et al. did not found any differences in the interferon associated depression regarding the gender of paticipants.[22,23] Similarly Fialho et al reported that age and gender had no significant effect and only baseline depression predicted depression at later time points.[26]

The findings of our study support and strengthen the hypothesis that interferon based therapies not only induce new depression but it also aggravates the scores of already existing depression and the high proportion of depression in patients receiving interferon therapy highlights the importance of recognition of this disorder while managing HCV infection.

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AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

Ali A: Main idea, study design, research work.

Babar AN: Manuscript writing.

Khan MA: Data analysis and followup.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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