PRE-TREATMENT ANXIETY AND INTERFERON INDUCED DEPRESSION IN HEPATITIS C PATIENTS

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ABSTRACT

Objective: To study the effect of pre-treatment anxiety on interferon induced depression in hepatitis C patients undergoing interferon treatment.

Methodology: Interrupted time series design was used for this study to assess at pre, in 2 follow up visits (after 24th and 48th week) and after completion of the treatment. The depression and anxiety of two groups of women (showing high and low pre-treatment anxiety score on the IPAT anxiety scale [PTAS]) was measured by the Siddiqui Shah Depression Scale (SSDS) and the IPAT Anxiety Scale. Female patients (n=57) being diagnosed for Hepatitis C and prescribed for interferon therapy were selected from three main hospitals of Peshawar, through convenience sampling technique.

Results: The age range of the sample was from 35 to 65 years (54.51+5.11 years). Compared to 25 % of the patients having low pre-treatment anxiety scores, 32 % of the patients with higher pre-treatment anxiety score experienced significant level of depression at week 24 and 48 during and after completion of the interferon treatment.

Conclusion: Pre-treatment anxiety has significant effect on the levels of depression, hepatitis C patients experience during and after completion of the treatment.

Key Words: Anxiety, Interferon alpha Therapy, Depression

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INTRODUCTION

Hepatitis C virus (HCV) is causing a major health problem on the global scale[1]. As a significant cause of liver diseases, it presents great challenges for patients, physicians, and counselors[2]. The rate of the disease is 2.2 to 03 % that is, approximately 130 to 170 million people worldwide have infected and three to four million are newly affected every year, resulting nearly 3,50,000 deaths per year[3]. According to a latest survey by Global Burden of Disease involving 117 countries (i.e., 90% population of the world) the most prevalent health problem worldwide is the hepatitis C (genotype1). This comprises 83. 4 million people around the world, out of which one third cases are in the East Asia and North Africa[4]. In some countries there are higher rates, for example, in Egypt (22 %) in Pakistan (4.8 %) and in China (3.2 %) prevalence rate has been reported[5].

The initial infection can progress to liver cirrhosis and cancer in 20 to 30 years[6]. The clinical complications of hepatitis C are anticipated to continue. About 20% chronic infected develop cirrhosis and 01 to 04% liver diseases. It is in fact a leading cause of liver transplantation in the Western countries[7].

Currently the advanced treatment approved by the Federal Drug Authority is the use of pro-inflammatory cytokine interferon-α (IFN-α) multidimensional protein in combination with a broad spectrum antiviral ribavirin (RBV) with increased rate of Sustained Virological Response (SVR) in 40 to 80 % of the patients[8]. Although it is an effective treatment but a profile of significant psychiatric side effects is associated with it which impact upon compliance[9-11]. Among all side effects depression is the most common and may occur in up to 60 % of the patients[12-13]. Besides, there is also incidence of anxiety due to IFN-α treatment which ranges between 1.4 to 3.3 %[14]. These neuropsychiatric side effects are the most common causes of discontinuation of the treatment[15].

Research has consistently reported the presence of anxiety, depression, psychosis, cognitive dysfunction and delirium among hepatitis C patients with IFN- α therapy[16-17]. Numerous studies demonstrate that prevalence of anxiety disorders in the hepatitis C patients

is as high as the depression[18-19]. Golden and Marie, in a study of hepatitis C patients using the Structured Clinical Interview for DSM-IV Axis I Disorders and current diagnosis found that 24 % of the patients had anxiety disorders in which panic and phobic anxiety disorder were the most common accounted for nearly half of the diagnosis[20]. In another study Hurlock (2001) examined the impact of pre-interferon anxiety in hepatitis C patients and found that IFN-α therapy worsen the symptoms of pre-existing anxiety[21]. Majer et al studied association between speed of motor responses and depressive symptoms in chronic hepatitis C patients prescribed to IFN-α treatment. Findings demonstrated that decreased motor speed was associated with increased symptoms of depression, anxiety, and fatigue in thepatients[22]. Gohier et al studied 71 chronic hepatitis C patients before, during and after the IFN-α therapy[23]. Each patient was assessed for anxiety and depression and the results revealed anxiety among these patients not only before but even after the discontinuation of the therapy[23].

According to a recent report, 18 million population of Pakistan have been infected with hepatitis, out of which seven million are infected with hepatitis B, and 11 million with hepatitis C. The disease is spreading rapidly due to the no availability of vaccine against hepatitis C, unscreened blood transfusion; reuse of the needles and syringes by health care providers, and sharing of the needles by intravenous drug users[5]. With this rate of national prevalence, Pakistan is currently facing an epidemic of viral hepatitis. The standard and successful treatment for HCV includes interferon alpha combined with oral ribavirin, but significant, behavioral, physical and psychiatric side effects are associated with it. The most common among them is the depression which has been reported by numerous researches[12-13]. Due to these side effects patients either reduce the dose or discontinue the therapy altogether. These side effects of the IFN-α treatment cannot be reduced because its mechanisms are unclear. However, targeting preventive measures are possible to alleviate the side effects by investigating the risk factors underlying the vulnerability. Keeping in view this reasoning the present research was designed to study the effect of one of the potential risk factors,that is, pre-treatment anxietyon the interferon-induced depression in hepatitis C patients.The conclusions derived from this study will have significant clinical implications in terms of neuropsychiatric safety of this treatment.

METHODOLOGY

Participants were recruited from hepatitis C patients scheduled for IFN-α therapy attending three main hospitals of Peshawar, namely, Khyber Teaching, Hayatabad Medical Complex and Lady Reading. Help of the concerned doctors and paramedical staff was requested in contacting the relevant patients, getting medical record of their disease and in the data collection. The data collection was started in December 2012 and completed in June 2014. The Siddiqui Shah Depression Scale (SSDS)[24] and the IPAT Anxiety Scale[25] were administered on each patient before the treatment in premises of the hospital at scheduled time. Those who obtained higher scores on SSDS were excluded. The logic behind this strategy was having participants with low scores on the depression scale. Two groups of patients that is, low depression and low anxiety scorers and low depression and high anxiety scorers were categorized on the basis of their pretreatment scores. Later on the sample was examined for their depression scores in 3 follow up visits, that is, at 24th, 48th weeks and after completion of the treatment. The pretreatment depression scores of the two groups, that is, high and low anxiety scorers were compared with their depression scores during the treatment (24th & 48th weeks) and post-IFN-α therapy depression.

RESULTS

The age range of the sample (n=57) was from 35 to 65 years (54.51$\pm$5.11 years). The mean pre IFN-α therapy SSDS score of high pre-treatment anxiety score (PTAS) group (n=32) was 25.25$\pm$7.15 with standard error of mean of 1.26 while the mean pre IFN-α therapy SSDS score of low PTAS group (n=25) was 13.92$\pm$1.75 with standard error of mean of 0.35. The results presented in table 1 reveal significant difference between high and low pre-treatment anxiety scorers in terms of depression at pre, 24th weeks, 48th weeks and post-IFN-α treatment. Patients having higher pre-treatment anxiety scores experience significant depression as compared to those with low pre-treatment anxiety scorers.

The results of Repeated Measure ANOVA across four time measurements for comparing Depression in High (F=4.68, p=0.03) and Low (F=0.08, p=0.77) Anxiety Scorers reveal significant difference in terms of depression in high and low anxiety scorers across four times measurements i.e., pre, after 24 weeks, after 48 weeks and post interferon therapy.

The mean pre IFN-α therapy anxiety scale score of high pre-treatment anxiety score (PTAS) group was 49.15$\pm$16.10 with standard error of mean of 4.55 while the mean pre IFN-α therapy anxiety scale score of low PTAS group was 22.85$\pm$9.42 with standard error of mean of 2.04. The results showing mean difference between Hepatitis C Patients with High and Low Pre-treatment Anxiety Scorers on IPAT Anxiety Scale at Pre, 24th Weeks, 48th Weeks and Post-IFN-α Therapy are expressed in table 2. The result of Repeated Measure ANOVA across four time measurements for comparing Anxiety in High-PTAS was F=42.10, p=0.000 and Low-PTAS was F=0.07, p=0.02.

Table 1: Mean Difference between Hepatitis C Patients with High and Low Pretreatment Anxiety Scores on SSDS at Pre, 24th Weeks, 48th Weeks and Post-IFN-α Therapy

	High-PTAS (n=32)				95%CI		Low- PTAS (n=25)				95%CI	
	M	SEM	t(df)	P	LL	UL	M	SEM	t(df)	P	LL	UL
At 24th Week	30.66 ± 15.84	2.80	1.81 (31)	.08	0.73	11.54	14.08 ± 8.65	1.73	.09 (24)	.92	3.40	3.72
At 48th Week	34.13± 44.38	7.84	2.83 (31)	.06	7.72	25.10	14.76 ± 14.17	2.83	.29 (24)	.77	3.50	3.83
Post-IFN-α	35.23 ± 44.38	7.84	2.84 (31)	.05	8.65	26.11	14.87 ± 14.17	2.84	29 (24)	.77	3.53	5.01

Note=IFN, Interferon, PTAS=Pretreatment Anxiety Scorers

Table 2: Mean Difference between Hepatitis C Patients with High and Low Pre-treatment Anxiety Scorers on IPAT Anxiety Scale at Pre, 24th Weeks, 48th Weeks and Post-IFN-α Therapy

	High-PTAS (n=32)				95%CI		Low- PTAS (n=25)				95%CI	
	M	SEM	t(df)	P	LL	UL	M	SEM	t(df)	P	LL	UL
At 24th Week	70.62 (19.20)	8.21	3.21 (31)	.00	0.22	12.25	31.78 (13.51)	4.31	2.13 (24)	.04	.31	12.23
At 48th Week	95.76 (21.87)	10.76	5.41 (31)	.000	0.27	16.17	36.10 (14.01)	4.37	2.22 (24)	.03	.35	15.43
Pre-IFN	49.15 (16.10)	4.55	10.27 (31)	.000	0.31	20.18	22.85 (9.42)	2.04	2.62 (24)	.01	.38	15.87

Note=IFN= Interferon, PTAS=Pre-treatment Anxiety Scorers

DISCUSSION

The results of this study suggest that hepatitis C patients with higher anxiety before the treatment experience significant level of depression during the course of therapy and thus are more vulnerable to IFN-α induced depression. These results are similar to the earlier researches which demonstrate that hepatitis C patients with higher baseline anxiety experience significant depression during the IFN-α therapy[21-23]. The incidence of anxiety during IFN-α treatment ranges between 1.4 to 3.3 %[14]. The results of the present study also reveal that participants having higher pre-treatment anxiety scored higher on the Anxiety Scale during and after completion of the treatment than those with low pre-treatment anxiety scores. In an earlier study, Hurlock et al examined the impact of interferon treatment on the baseline anxiety in hepatitis C patients and found that IFN-α therapy worsen the symptoms of pre-existing anxiety[21].

Researchers have studied anxiety in patients having positive hepatitis C virus at baseline and after completion of the treatment[26]. Findings revealed a significant increase in anxiety of these patients[26]. Similar result was reported by Musselman et al[27]. Another study evaluated risk factors in hepatitis C patients[28]. Their result showed that female gender, baseline anxiety symptoms, increased in dose of the interferon and longer time duration of the therapy as the most important in the development of depression during the treatment[28]. Castellvi et al studied baseline depression, anxiety, past history of mood disorders and personality factors (i-e, low self-directedness, fatigability & disorderliness) in a cohort of 204 hepatitis C outpatients. Patients were assessed using standardized instruments at baseline, and at 4th, 12th, 24th, and 28th weeks of the therapy[29]. Result demonstrated low self-directedness, past history of mood disorders and baseline depression and anxiety as independent predictors of high levels of depression in

these patients during the antiviral therapy[29].

Santos et al examined the incidence and risk factors of depression and anxiety during pegylated interferon plus ribavirin among 176 chronic hepatitis C patients[30]. Depression and anxiety of the patients were assessed at baseline and after 4th, 12th, and 24th weeks of the therapy. Findings revealed that higher baseline anxiety scores, primary education and being an immigrant were significantly associated with the depression during the treatment. Patients having higher baseline depression and anxiety scores had poor adherence[30]. Scalori et al in their study assessed the initial states (i.e., before treatment) in hepatitis C patients and found that those who obtained a certain cut off scores on the MMPI and the Montgomery Asberg Depression Rating Scale were more likely to developed anxiety and depression during the treatment than those having below cut off scorers[31]. Kraus et al in a longitudinal study examined depression, anxiety and anger/hostility in 104 chronic hepatitis C patients[32]. The participants were divided in treatment (n=84) and control group (n=20). Findings revealed that compared to the control group patients in the treatment group experienced significantly levels of depression, anxiety and anger/hostility during the treatment. The cumulative frequency of emotional distress, that is, depression, anxiety and anger/hostility was 57.7 % during the treatment, compared to 22.5 % pretreatment[19].

Hepatitis C like any chronic disease is associated with an increased risk of psychiatric disorders; the most common among them is the depression. The neuropsychiatric side effects of the IFN-α therapy have been documented by many studies[13, 22, 32-34]. These adverse side effects have significant influence on the course of treatment, with dose reduction, or some time discontinuation of the therapy. Several researches established that depression induced by interferon treatment can be effectively treated with antidepressants[35]. However, researches demonstrate that as a drug, the antidepressants are in fifth rank in terms of causing liver damage[36]. Keeping in view of these findings, some researchers tried to find effective psychological therapies for the treatment of pre-interferon depression. For example, Elsafy et al in a recent study examined the role of Cognitive Behavior Therapy in 100 hepatitis C patients and found CBT to be an effective technique for the treatment of baseline depression[37]. Similar findings have been reported by others studies[38-39].

CONCLUSION

It can be concluded that pre-treatment anxiety has significant effect on the levels of depression and anxiety, hepatitis C patients experience during and after completion of the treatment. The study has important implications on part of the clinicians to introduce an effective psychological treatment program for the hepatitis C patients before initiating interferon therapy to get maximum clinical benefits.

IMPLICATIONS

Patients with clear symptoms of anxiety should be subjected to adequate psychological therapies before the IFN-α treatment in conjunction with biological therapies (such as anti- depressants). Patients being diagnosed with anxiety disorders prior to treatment should be regularly evaluated during the entire course of therapy and if seems essential, psychological treatment should continue, as long as it is required.

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CONTRIBUTORS

SA and NS conceived the idea, planned the study, and drafted the manuscript. FJ supervised the study. All authors contributed significantly to the submitted manuscript.