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FREQUENCY OF ADVERSE EFFECTS OF INTERFERON TREATMENT IN HEPATITIS C PATIENTS

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ABSTRACT

Objective: Frequency of adverse effects of interferon treatment in Hepatitis C Patients. **Study design:** Cross sectional descriptive study. **Period:** Six months setting: Departments of Medicine, Liaquat University of Medical and Health Sciences Jamshoro/ Hyderabad. **Material & Methods:** 280 patients of hepatitis C undergoing treatment with alpha Interferon were included in the study. Continuous variables such as age, duration of disease, duration of Interferon, were computed as *(Mean ± Standard Deviation).* Categorical variables such as patient sex, adverse effects such as anemia, neutropenia, thrombocytopenia, hyperthyroidism, hypothyroidism after therapy was presented as frequency and percentage. Post -stratification chi- square test was applied. $P<0.05$ was taken as significant. The SPSS software version 20 was used for data analysis and evaluations. **Results:** In our study of 280 patients, the gender distributions was assessed; male 118 (42.1%) and females 162 (57.9%). The mean duration of Interferon treatment was 4.4 months. Hematological adverse effects were assessed and 91(32.5%) patients had neutropenia and 189(67.5%) had normal neutrophil count. The mean level of hemoglobin was 10.3mg/dl, minimum hemoglobin level was 5.00 mg/dl and maximum level was 14.00 mg/dl. Thrombocytopenia was found in 122(43.6%) of patients as per diagnostic criteria. 21 (7.5%) of patients had developed hyperthyroidism. Body Mass Index of the patients were evaluated. Mean BMI of study population was 26.05 Kg/m^2 with Std. deviation of 5.6378 Kg/m^2. Minimum BMI was $15Kg/m^2$ and maximum BMI was 40 Kg/m^2. **Conclusion:** The frequency of adverse effects of Interferon therapy in patients of hepatitis C is an important aspect to be considered. This study suggests that hematological adverse effects are common with Interferon therapy in patients of Hepatitis C.

Key words: Interferon therapy, hepatitis C, anemia, thrombocytopenia.

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INTRODUCTION

Hepatitis C is a common blood born viral infection in Pakistan. About

170 million people are affected by this infection worldwide. Prevalence of Hepatitis C viral infection is estimated to be around 3 % of the population in Pakistan.[1] Chronic hepatitis C is associated with complications such as cirrhosis of liver and it can lead to hepatocellular carcinoma. In Pakistan genotype 3 is found to be the most common genotype.[2]

Antiviral drugs used in treatment of hepatitis C i.e. Pegylated Interferon which are Peg Interferon alfa-2a and Peg Interferon alfa-2b are associated with better clinical outcomes including lesser frequency of side effects and improved antiviral efficacy.[3,4]

Interferon is associated with number of side effects which include generalized symptoms as well as hematological, endocrinological, dermatological and neuropsychiatric symptoms. Hematological side effects include anemia, neutropenia and thrombocytopenia. Apart from side effects which are developed during treatment, dose reduction and poor compliance are major concerns for the prognosis of these patients.[5]

Epidemiology of hepatitis C infection

The global epidemic of HCV infection affects approximately 200 million individuals worldwide HCV prevalence in Pakistan is much higher when compared to the other neighboring countries of the region like India where the incidence is 0.9% and China where incidence is reported to be 3.2%.[6]

Incubation Period: The incubation period of Hepatitis C infection is between 6-7 weeks[8]

Exposure It is blood born infection which is caused by exposures such as transfusion and unsafe injections. One of the observations regarding HCV infection is that in about eighty five percent of patients with newly infected a persistent infection develops. While in number of patients, hepatitis many occur with or without evidence of chronic hepatitis.

Transmission A number of routes of infection have been identified which are as following.[8]

1. Unsafe injection
2. Unscreened blood transfusion
3. Poor infection control practices
4. Piercing and tattooing

It has been observed that approximately forty percent of all new cases are infected by these routes of transmission. [10].

OBJECTIVE

The objective of study was to ascertain frequency of adverse effects of Interferon based treatment in patients with hepatitis C.

MATERIAL AND METHODS

Study design: Cross sectional descriptive study.

Setting: Departments of Medicine, Liaquat University of Medical and Health Sciences, Jamshoro/ Hyderabad. Duration of study: Six months from Dec 2012 - May 2013.

Sample size*:* The sample size for the study was calculated by the formula for single proportions. The prevalence of side effects is estimated to be 3%, margin of error is 2% and confidence interval is 95%. Sample size is 280.

Sampling technique: Non-probability consecutive.

Inclusion criteria:

1. All above the age of 18 years of either gender with positive detectable serum HCV.
2. All patients on Alpha Interferon treatment.
3. Patients giving consent to be included in the study.

Exclusion criteria:

1. Co-infection with hepatitis B.
2. Pregnancy.

Data Collection Procedure

The source of data were the patients of Hepatitis C undergoing treatment with alpha Interferon as per inclusion and exclusion criteria attending OPD or admitted in medical department of Liaquat University of Medical and Health Sciences Hospital, Jamshoro/ Hyderabad.

Patients were evaluated by history, examination and laboratory investigations. Blood sample for complete blood count and level of TSH was taken in a test tube containing no preservative. This was sent in half an hour to Liaquat University Hospital laboratory and done by the qualified pathologist. These tests were done free of cost.

A questionnaire was filled describing demographic and clinical findings. Each patient's diagnostic categorization was recorded according to operational definition.

Data Analysis Procedure

Continuous variables such as age, duration of disease, duration of Interferon, were computed as *(Mean ± Standard Deviation)*. Categorical variables such as

patient's sex, adverse effects such as anemia, neutropenia, thrombocytopenia, hyperthyroidism, hypothyroidism after therapy was presented as frequency and percentage. The Effect modifiers such as age, gender, BMI was controlled by stratification. Post -stratification chi- square test was applied. P<0.05 was taken as significant. The SPSS software version 20 was used for data analysis and evaluation.

Ethical consideration

1. Informed consent was taken from the patients admitted in Department of Medicine, Liaquat University Hospital, Jamshoro/ Hyderabad.
2. The rules of ethical committee of Liaquat University of Medical & Health Science Jamshoro/ Hyderabad were followed.

RESULTS

In our sample of 280 patients, the gender distribution was assessed; male 118 (42.1%) and females 162 (57.9%) (Table 1). The mean age was 35.5 years, Std.deviation 9.02 years, the minimum age was 18 years and the maximum age in the study population was 65 years (Table 2).

The mean duration of Interferon treatment was 4.4 months, with median duration 4.47 months, the Std.deviation was 00.84 months, the minimum duration of the treatment was 2 months and the maximum duration of the treatment was 7 months (Table 3). Duration of the Interferon therapy assessed and it is found that 99 (35.4%) patients were taking Interferon therapy for 5 months, 89 (31.8%) patients were taking Interferon for 4 months and only one patient was taking for 7 months (Table 3). In this study sample of 280 patients, the duration of disease was assessed and it is found that the mean duration of the disease was 17 months, with Std. deviation at 11.7 months, the minimum duration of hepatitis C was 2 months whereas the maximum duration of the disease was 84 months (Table 4).

Hematological adverse effects were assessed and the number of neutrophils in the patients was analyzed and the mean number of neutrophils was 1538 with Std. deviation at 553.11, the minimum number of neutrophils was 500 and the maximum had 2700 neutrophils (Table 5).As per diagnostic criteria neutrophil count less than 1500 were labeled as neutropenia. In this study group, 91 (32.5%) patients had neutropenia and 189 (67.5%) had normal neutrophil count. The chi-Squire test was applied for group of patients having neutropenia and duration of Interferon treatment and it was found the p value at 0.0037 which shows that in this study group, neutropenia was statistically significantly associated with duration of Interferon therapy.

In this study population, level of TSH was assessed. The mean level of TSH is 4.00 mu/L, minimum TSH level was 0.01 and maximum level is 35.00 mu/l. The number of patients diagnosed of hyperthyroidism is 21(7.5%).p value is 0.068, which shows no significant association of duration of Interferon therapy and hyperthyroidism.

The number of neutrophils in the patients was analyzed and the mean number of neutrophils was 1538 with Std. deviation at 553.11, the minimum number of neutrophils was 500 and the maximum was 2700 neutrophils (Table 5). As per diagnostic criteria, neutrophil counts less than 1500 were labeled as neutropenia. In this study group, 91 (32.5%) patients had neutropenia and 189 (67.5%) had normal neutrophil count. The chi-Squire test was applied for group of patients having neutropenia and duration of Interferon treatment and it was found the p value at 0.0037, which shows that in this study group, neutropenia was statistically significantly associated with duration of Interferon therapy.

In this study population, level of Hemoglobin was assessed. The mean level of Hemoglobin was 10.3 mg/dl, minimum Hemoglobin level was 5.00 mg/dl and maximum level was 14.00 mg/dl. The number of patients diagnosed with anemia was 128 (45.7%). p value is 0.0048, which shows significant association of duration of Interferon therapy and anemia.

The number of platelets in the patients was analyzed and the mean number of platelets was 152571 with Std.deviation at 79742, the minimum number of platelets was 30000 and the maximum was 392000 (Table 5). As per diagnostic criteria, platelet count of less than 150000 was labeled as thrombocytopenia. The number of patients having thrombocytopenia as per our diagnostic criteria was 122 (43.6%). Chi-Squire test was applied and p value is 0.0079, which shows a statistically significantly association with duration of Interferon therapy and thrombocytopenia.

Body Mass Index of the patients was evaluated, mean BMI of study population was 26.05 Kg/m^2 with Std. deviation of 5.6378 Kg/m^2 Minimum BMI was 15Kg/m^2 and maximum BMI was 40 Kg/m^2.

TABLE NO. 1
GENDER DISTRIBUTION
N=280

GENDER	FREQUENCY	PERCENT
Male	118	42.1
Female	162	57.9
Total	280	100

TABLE NO. 2
AGE DISTRIBUTION

S. No.	AGE DISTRIBUTION	YEARS
1	Mean	35.5
2	Std.Deviation	9.02
3	Minimum	18.0
4	Maximum	65.0

TABLE NO. 3
DURATION OF INTERFERON THERAPY

DURATION WEEKS	FREQUENCY	PERCENT
1-5	147	52.4
5- 10	132	47.2
More than 10	1	.4
Total	280	100.0

TABLE NO. 4
DURATION OF DISEASE

DURATION OF DISEASE (MONTHS)	NUMBER OF PATIENTS	PERCENTAGE
1-9	74	26.42
10-19	81	28.92
20-29	24	8.47
30-39	33	11.78
40-49	46	16.42
More than 50	22	2.66

TABLE NO. 5
HEMATOLOGICAL COUNTS

S. No.	Characteristics	Hematological counts	
		Mean	St.deviation
1	Hemoglobin	10.3gm/dl	2.40gm/dl
2	Neutophils	1538 mm^3	553 mm^3
3	Platelets	152571 mm^3	79042 mm^3

DISCUSSION

Interferon therapy for Hepatitis C is associated with number of side effects. The objective of this study was to assess adverse effects of Interferon therapy in hepatitis C patients. The most common adverse effects observed in this study were hematologic abnormalities, including anemia, neutropenia and thrombocytopenia. Other adverse effect included thyroid dysfunction such as hyperthyroidism. In this study, an assessment of frequency of adverse effects of Interferon therapy was analyzed and the results suggested that in the selected patients of Hepatitis C which have taken Interferon therapy, the adverse effects were present.

A number of factors have been theorized to predict the development and/or progression of adverse effects in hepatitis C patients. These adverse effects have been examined in several clinical studies that attempt to determine which ones are the most influential, with relatively consistent results. The factors that most seem to agree on are as follows: duration of disease, duration of Interferon therapy and genotype of HCV.

Our sample consisted of 280 patients between the ages of 25 and 55 years and above. There was an almost even distribution in gender, with male 42.1% and females 57.9%.The mean age of the entire study population was 35.5 years. The mean duration of the disease was 17 months; the minimum duration was 2 months whereas the maximum duration of the disease was 84 months. Duration of the Interferon therapy was assessed and it is found that 35.4% patients were taking Interferon therapy for 5 months 31.8% patients were taking Interferon for 4 months and only one patient was taking for 7 months.

In this study group, 91 (32.5%) patients had neutropenia. When analysis of relation of neutropenia and gender was carried out which shows that among 118 males, 32 had developed neutropenia with Interferon

treatment and among 162 women, 59 developed neutropenia. Statistical analysis by applying Chi-square test indicated a non significant association of neutropenia in relation to gender.

The incident of neutropenia in patients taking Interferon therapy is in accordance to other studies as well as where hematological adverse effects were observed. Kowdley has investigated the side effects of Interferon therapy and found that there was a high incidence of hematologic side effects with this therapeutic regimen. Hematologic side effects were particularly common; bone marrow suppression caused by Interferon may result in neutropenia and thrombocytopenia, which is evident from this study as well. In this study population, the numbers of patients diagnosed of anemia were 45.7% with p value is 0.0048, which shows significant association of duration of Interferon therapy and anemia.[13, 19]

Patients having thrombocytopenia as per our diagnostic criteria were 43.6%. Statistically significantly association with duration of Interferon therapy and thrombocytopenia was found in this study which is reported in other studies.[18] Level of TSH was assessed. The number of patients diagnosed of hyperthyroidism is 7.5%.p value is 0.068, which shows no significant association of duration of Interferon therapy and hyperthyroidism. However a number of studies has reported thyroid dysfunction with positive results.[54,72] In a retrospective multicentric study by Fred [17] it was found that Eighty (34%) individuals showed an episode of severe hematological toxicity. Severe anemia, neutropenia and thrombocytopenia occurred in 32 (13%), 42 (18%) and 26 (11%) patients, respectively.

This study suggests that hematological adverse effects are common in patients of Hepatitis C taking Interferon therapy. This inference is reported by other studies as well.[19]

CONCLUSION

The frequency of adverse effects of Interferon therapy in patients of hepatitis C is an important aspect to be considered. These adverse effects cause either abrupt antiviral treatment termination, leading to increased rates of unsuccessful therapies. Hematological adverse effects present during Peg IFN combination therapy, result in decreased levels of hemoglobin and platelet counts. This study suggests that hematological adverse effects are common in patients of Hepatitis C with Interferon therapy.

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The Operational definitions:

· Hepatitis C: Positive PCR for HCV RNA will be labelled as hepatitis C positive.

Adverse effect:

· Anemia: When Hemoglobin becomes < 10 g/dl will be labelled as anemia

· Neutropenia: When neutrophils count <1500cells/ul will be labelled as neutropenia.

· Thrombocytopenia: When platelets count < 150,000ml will be labelled as thrombocytopenia.

· Hyperthyroidism: When Tsh =<0.2mU/L will taken as hyperthyroidism.[13]

· Hypothyroidism: When Tsh>5mU/L will be taken as hypothyroidism.[14]

Authors contribution:

* Focal person to conduct research and article management ** Supervision of project and critical review and data collection

*** Collection of Samples, Data Analyysis.

Conflict of interest: No conflict of interest