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ORIGINAL ARTICLE

Comparison of Impairment of Pulmonary Function Test due to Plain Versus Pegylated Interferon Therapy in patients with Chronic Hepatitis C Virus Infection

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ABSTRACT

Aim: To compare Impairment of pulmonary function tests due to plain versus pegylated interferon therapy in the diagnosed cases of chronic Hepatitis C

Methodology: In this comparative study, 71 patients fulfilling inclusion criteria were randomly included in each group. Study consisted; Group 1 (Control Group): Pulmonary Function Tests performed before and after the completion of 24 weeks of treatment with Plain/conventional Interferons and ribavirin. Group 2 (experimental Group): PFTs performed before and after the completion of 24 weeks treatment with Pegylated Interferon Therapy and ribavirin. Referred patients of both groups underwent spirometry (PFTs) at baseline and at the end of 6 months

Results: Mean value observed for age was 49.86, for height 1.592 meters, for weight 62.6 kg and for BMI 24.9. Before and after therapy mean for FEV1 was 90.19 and 67.71 and it was 91.34 and 67.83 for FVC respectively. N=71 patients were enrolled in both groups. Male gender showed high prevalence 70%. Group-1 (46 vs 25) & group-2 (45 vs 26) male to female ratio seen. Adult age group hold bulk of disease (30 - 40 years of age). Patients preferred winter season for treatment (Sep to Nov). Low viral load and genotype 3a were common findings (82% and 35%). Constitutional symptoms improved after therapy (86 to 44%) as a whole. Individually, anorexia, body aches, lethargy and fever were like this (39 vs 19%, 66 vs 28%, 54 vs 30%, 19 vs 11%) pre and post therapy. Cough and dyspnea reported in 7% and 20% respectively.

Conclusion: According to the present study, treatment with pegylated interferon and ribavirin is associated with impairment of pulmonary function tests similarly as treatment with plain interferon and ribavirin. Long Half-life of pegylated interferon cause more impairment in lung functions as indicated by limited available literature (Foster GR et al).

Keywords: Chronic hepatitis C, Pulmonary function tests, plain/Conventional interferon therapy, Pegylated interferon therapy.

INTRODUCTION

Takamizawa et al states, "Hepatitis C is a common viral infection that spreads via blood borne route. It causes body aches, arthralgia and weakness at the beginning and most of the time progresses into the decompensated chronic liver disease that is associated with notorious complications like ascites, encephalopathy and variceal bleed etc. Hepatologist treats chronic Hepatitis C with interferons nowadays, but literature shows that this treatment modality impairs pulmonary functions as measured with Spirometry[1]. We planned to compare both modalities of interferon therapy (plain & pegylated) regarding PFTs impairment. Local evidence was missing at all in this regard, so, we conducted this study**.**

The objective of the study was to compare impairment of pulmonary function tests due to plain versus pegylated interferon therapy in the diagnosed cases of chronic hepatitis C.

Hypothesis: Pegylated interferon therapy causes more impairment in pulmonary functions as compared to plain interferons in chronic hepatitis C.

Operational definition:

Chronic Hepatitis C: Qualitative PCR positive for Hepatitis C virus RNA.

Impairment of PFTs: If any one of FEV1, FVC or FEV1/FVC became impaired i.e. value of FEV1 is below 80% of predicted value, value of FVC is below 80% of predicted value or value of FEV1: FVC ratio is above eighty percent

METHODOLOGY

The randomized control study (comparative interventional design) was conducted in OPD of Medicine, Mayo Hospital, Lahore during one year period after IRB permission. I took expected percentage of difference in FVC before and after therapy (13%-6%=7%). Sampling technique used was non-probability n purposive

Using McNemar`s test

$$n = Z^2_{1-\alpha/2} P (1 - P) / d^2$$

Where;
n = sample size
Z^2 1-α/2 = 1.96 (for 95% conf. level)
Z^2 1-α /2 = 2.70 (for 90% conf. level) (adjusted by software)
P = size of effected population= 07%
d = absolute precision/margin of error = 05%
By putting values;

$$n = \frac{2.70 \times 0.07(1 - 0.07)}{0.05 \times 0.05}$$

$$n = \frac{2.70 \times 0.0651}{0.0025} \qquad n = 70.308 = 71$$

This was the sample size for pegylated interferon therapy. As data regarding the affected population due to plain interferon therapy was not available in the literature, so sample size of 71 also assumed true for plain interferon therapy.

Inclusion criteria:

- Based upon operation definition (exclusively)
- Both male and female patients
- 18 - 70 yrs.
- Positive PCR for HCV RNA

Exclusion criteria:

- Past pulmonary diseases (documentation of pulmonology department) e.g., COPD, Asthma, ILD, Pulmonary T.B, Pulmonary hypertension etc. (Symptomatic and diagnosed cases)
- Patients with co-infection of HBV and HIV
- Smokers (with smoking history of 10 or more pack year).
- Patients on steroid therapy.
- Patients with history of Hakeem medication in last 6 months.
- Patients with cough, dyspnea and fever dealt with as per operational definitions
- Intravenous drug abusers.
- Patients with contraindications to the interferon therapy e.g.; CCF), severe depression and psychosis, organ transplant, pregnancy, cirrhosis, malignancy, thyroid diseases, neoplasia, thrombocytopenia etc.
- Patients who refused consent.

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Data collection procedure: Seventy-one cases (each for plain and peg. INF therapy) fulfilling inclusion criteria included in the study. Two Groups made. Group with patients taking Plain interferon therapy labelled as A while group with patients on pegylated interferon therapy labelled as B. Written informed consent obtained. Complete home address with telephone no was recorded to make sure the follow up visit on a separate proforma (attached). Age, height and weight recorded as quantitative variables while sex as qualitative variable. PFTs performed after procedure demonstration using a single machine. PFTs were the primary outcome variables. PFTs done before and after 6 months of therapy. Plain interferon therapy @ 03 million units subcutaneous thrice weekly and Pegylated interferon therapy @ 180microgram subcutaneous once weekly for six month was given along with ribavirin in both groups.

Data analysis: SPSS version 23 used for statistical analysis. Mean and standard deviation were age and height (as Quantitative Variables.). Frequency and percentages were sex and PFTs impairment (as Qualitative variables.). Quantitative McNamar described pre and post treatment PFTs. P-value was < 0.05.

RESULTS

A. Restrictive lung pattern

Table 1: Restrictive lung pattern & shortness of breath after therapy

Shortness of breath after treatment	FVC		Total
	Not Significant	Significant	
Observed	25	4	29
Not observed	96	17	113
Total	121	21	142

21 patients developed restrictive lung pattern after interferon therapy, out of which only 04 patients were short of breath.

Note: although total 29 patients (20%) developed shortness of breath as per history (post treatment), out of which cause of dyspnea:

Was restrictive lung disease/pattern in 4

Was obstructive lung disease/pattern in 2 patients

In 23 patients, cause was unknown. PFTs were normal

B. Obstructive lung patterns

Table 2: Obstructive lung pattern & shortness of breath after Interferon therapy

shortness of breath after treatment	FEV1		Total
	Not Significant	Significant	
observed	**27**	**2**	**29**
not observed	103	**10**	113
Total	130	**12**	**142**

12 Patients developed obstructive lung pattern after interferon therapy, out of which only 02 patients were short of breath.

C. Interconversion of lung patterns

Table 3: Restrictive lung pattern in HCV patients changed into obstructive pattern after Interferon

FEV1	FVC		Total
	Not Significant	Significant	
Not Significant	113	**17**	130
Significant	**11**	**1**	**12**
Total	124	**18**	**142**

18 patients already had asymptomatic lungs restriction, noticed at Pulmonology department while screening such patients through PFTs.

01 of these patients developed obstructive lung pattern after interferon therapy.

17 patients showed other results after initial restrictive lung pattern.

11 new cases observed to develop obstructive lung pattern post therapy 5 patients already had asymptomatic lung obstruction.

21 cases were observed to develop lung restriction after interferon therapy, as above. [10]

Table 4: Obstructive lung pattern after HCV changed into restrictive pattern after interferon

Post therapy FVC	FEV1 after HCV		Total
	Not Significant	Significant	
Not Significant	116	**5**	121
Significant	**21**	**0**	**21**
Total	137	**5**	**142**

Table 5: T-Test

Parameters observed	interferon administered	N	Mean	Std. Deviation	P value
FEV1 after therapy	plain	71	82.89	7.003	**0.001**
	peg	71	78.52	8.080	
FVC after therapy	plain	71	92.04	6.896	**0.000**
	peg	71	84.93	9.083	

p value was significant (n= 0.000 & 0.001), therefore alternate hypothesis H1 proved. This means that pegylated interferon results in more impairment in pulmonary functions as compared to plain interferon

DISCUSSION

I compared Impairment of pulmonary functions into 02 groups due to plain versus pegylated interferon therapy in chronic hepatitis C. My **hypothesis** was that pegylated interferon therapy causes more impairment in pulmonary functions as compared to plain interferons in chronic hepatitis C[2].

Mean value observed for age was 49.86, for height 1.592 meters, for weight 62.6 kg and for BMI 24.9. Before and after therapy mean for FEV1 was 90.19 and 67.71 and it was 91.34 and 67.83 for FVC respectively

Maximum patients seeked treatment during the months of September to November. Many patients expressed a myth that drugs for hepatitis C treatment are hot and these should be taken in the winter season.

Hepatitis C is more common during the age 30 – 40 years. It may be due to screening before blood transfusions. Early age spike ranging from 20 – 30 years was also common, owing to screening at college/universities. Other random distribution was due to screening during the evaluation for other comorbidities[13].

Hepatitis C mainly affects male gender as proved. 70% patients were male. It may be because of more exposure. Barbers may play a vital role in this regard. IV drug addiction is also an issue of male gender in our population. Homosexuality may be another cause[3].

Eighty two percent patients bearing low viral load. Hospital lab-based genotype prevalence was 3a, non-typeable, genotype 3,3b,2,1 and 4 (35,18,17,14,8,4 and 3.5%) respectively. Viral load-based genotype prevalence was also same. “Lost follow-up patients” and “not achieved SVR patients” were frequent (21 vs 16 and 12 vs 10 respectively) where we used plain interferon therapy whereas “SVR achieved patients” were more (45 vs 36) where we used pegylated interferon therapy with less follow up loss (10 vs 12).

Constitutional symptoms (anorexia, body aches, lethargy and fever), as a whole, improved in 50% of patients after treatment as per history given by the patient. Individual symptoms also improved after therapy when analyzed with leading questions in majority of the patients. Constitutional symptoms as a whole (86 to 44%) and specific symptoms including anorexia (39 to 19%), body aches (66 to 28%), lethargy (54 to 30%) and fever (19.01 to 11.2%) improved after therapy. Statistically insignificant difference noted in fever from baseline to 6th month follow up (p-value=1.000 & 0.648 respectively). Vinod K Dhawan showed body aches in 15% patients after HCV infection While Mann’s et al shared data indicating anorexia 21%, body aches 42%, lethargy 54% and fever 43% after peg interferon therapy[5].

Cough noticed in 10 patients (7%) that was occasional. Out of these 04 were having abnormal lung pattern (2.81%) as

mentioned in dyspnea. Rest of them were normal. Anti-tussive given and referred to pulmonology department for follow up. Statistically insignificant difference noted in cough from baseline to 6th month follow up. i.e., (p-value=0.215, 0.322 respectively). Foster GR et al noticed cough in 24% vs 26% cases during (Alb vs Peg) INF therapy.[02] While Brown K et al depicted 28.4 % cases developing cough during peg interferon therapy[9]

History of dyspnea was positive in 29 patients (20.42%) after interferon therapy. Only 06 patients showed abnormal lung pattern on PFTs. Out of these, only 04 were having mild exertional dyspnea. These patients referred to pulmonology department for further evaluation. Insignificant difference noted statistically. (P value=0.171 & 0.362 respectively). Foster GR et al noticed dyspnea in 11% vs 14% cases during (Alb vs Peg) INF therapy.[02] While Brown K et al depicted 17.8% cases developing dyspnea during peg interferon therapy[9]

Now we are well aware of INF induced lung insult. It may be mild usually. It can also cause severe insult e.g., restrictive lung diseases

Eighteen cases (12.67%) were having restrictive lung pattern at the time of start of therapy. At the completion of INF therapy, 14 patients (9.85%) showed normal results out of them, 03 patients (2.11%) continue to have restrictive lung pattern, while 01 case (0.7%) developed obstructive lung pattern. Restrictive lung pattern observed in 21 cases (14.78%) after interferon therapy. This includes 3 old and 18 new cases (12.67%). These 21 patients and one patient who developed obstructive lung pattern after interferon needed follow-up on long-term basis that was beyond the scope of current study about interferon related lung diseases and their complications. Clinically only 04 patients (2.81 %) were short of breath. Erturk et al noticed low FEV1/FVC and FVC in 55% and 15% patients, respectively.[1] Foster GR et al noticed low FVC in 17% vs 06% cases during (Alb vs Peg) INF therapy on average.[02] Foster also depicted low FVC in 6% cases at baseline. FVC further deteriorated to 8 % cases at 12 weeks of peg interferon therapy. No improvement noticed and value settled at 13 % after 6 months of therapy completion. Concisely, 7 % patients developed restrictive lung pattern after interferon therapy.[02] Brown K et al depicted low FVC in 5.8% cases at baseline. FVC further deteriorated to 23.1% cases at 12 weeks of peg interferon therapy. Improvement noticed and value settled at 12.9 % after 6 months of therapy completion. Briefly, 7.1% patients developed restrictive lung pattern after interferon therapy[9] Ferrari C et al noticed predominantly lung restriction in his studied HCV positive patients. Helmy N.A et al noted FVC (below 80% of predicted values) in 20% cases[11]

Although total 29 patients (20.4%) complained of shortness of breath after treatment. Cause of shortness of breath was restrictive lung pattern in 04 patients (2.81%), obstructive lung pattern in 02 patients (1.4%) and "personal perception" in 23 patients (16.19%). Pulmonary functions remained normal in third case.

Only 05 patients (3.52%) were having obstructive lung pattern at the time of start of therapy. None of them was short of breath and all of these developed normal

PFTs after completion of therapy, 12 patients (8.45%) developed obstructive lung pattern after interferon therapy, out of which only 02 patients (1.4%) were short of breath. 1(0.7%) of these 12 cases developed obstructive lung pattern who was restrictive at start of therapy, while 11 cases were new (7.74%). These 12 patients not investigated due to no long-term follow up as it was beyond the scope of current study. All patients who were short of breath or who showed any abnormal lung pattern referred to pulmonology department for further workup. Erturk et al noticed low FEV1/FVC and FEV1 in 55% and 25% patients, respectively[1]. Foster GR et al noticed low FEV1 in 8.8% vs 8.1 % cases during (Alb vs Peg) INF therapy on average.[02] Foster also depicted low FEV1 in 11% cases at baseline. FVC further deteriorated to 12.1% cases at 12 weeks of peg interferon therapy. No improvement noticed and value settled at 13% after 6 months of therapy completion. Concisely, 2% patients developed obstructive lung pattern after interferon therapy[2]. Jonathan et al noted very low FEV1 after HCV infection[8]. Brown K et al depicted low FEV1 in 10.5% cases at baseline. FEV1 further deteriorated to 26.4 % cases at 12 weeks of peg interferon therapy. Improvement noticed and value settled at 13.2% after 6 months of therapy completion. Concisely, 13.2% patients developed obstructive lung pattern after interferon therapy [9] *Helmy N.A et al noted* FEV1 (below 80% of predicted values) in 20% cases[11]

P value was significant (n= 0.000 and 0.001) for restrictive and obstructive lung pattern respectively, therefore alternate hypothesis proved. This means that pegylated interferon cause more impairment in pulmonary functions as compared to plain interferon[2].

Peg INF is still superior as compared to plain due to many reasons

- Clinically significant impairment of PFTs is so small in frequency that it is negligible once weekly dose convenience
- More virus clearance rate (SVR achieved)
- Less recurrence rate of infection
- Less loss of follow-up
- Moreover, new treatment modalities being searched out due to limitations in IFN therapy (peg INF causes impairment in pulmonary functions while plain INF therapy is not convenient for the patient due to multiple doses schedule, less virus clearance rate and high recurrence rate of infection). Therefore, treatment with peg INF is still an option with an eye upon looking the future of hepatitis C treatment without INF therapy[4]

Government based setups: This was the era when international community was discussing use of oral anti-virals, creating confusion regarding use of INFs due to its side effects and we were bound to create a space for interferons till the availability of oral anti virals in our Government setups for poor patients. As, this study proved little percentage of impairment in PFTs and more little percentage of clinical cases of shortness of breath as well. Therefore, I declare interferons whether plain or pegylated, they are safe for use[6].

Recommendations: Students of clinical medicine are directed to explore complications of impairment in PFTs in these patients while performing follow-up in remote future with an eye upon radiological implications of disease that will be very helpful in making further decisions regarding continuation of the current interferon therapy. Moreover, variety of lung diseases will be stratified after intervening these patients through HRCT in remote future.[7] There are equal chances of disappearance of impairment in PFTs and reversal of tissue disease as well based upon 6-month follow up results of my study. We observed a big percentage 16% of patients who complained of shortness of breath but having normal lung functions. Therefore, students are also directed to observe level of cytokines in those patients who are not having abnormal PFTs and explore level of their release and type of markers as well[7].

Limitations: Limitations of my study are loss of follow up of a significant no of cases. No "blinding" applied while selecting the cases through OPD. Percentage of error kept 5% with 95% precision rate. Scope of interferon diminished, rather almost obsolete now. It was unpredictable for me while conducting the study. As alternate hypothesis approved, so results are affecting the clinician's decision regarding selection of interferon therapy. However, students of clinical medicine can utilize the results in order to select further research directions in this subject.

CONCLUSION

According to the present study, treatment with pegylated interferon and ribavirin is associated with more impairment of pulmonary function tests as compared to treatment with plain interferon and ribavirin. Long half-life of pegylated interferon caused more

impairment in lung functions as indicated by limited available literature.

Conflict of interest: Nil

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