TYPES AND PREDICTORS OF INTERFERON/RIBAVIRIN INDUCED CARDIAC COMPLICATIONS IN THE EGYPTIAN PATIENTS WITH CHRONIC HEPATITIS C VIRUS

Ibtesam I El-Dosouky, M.D.*, Soha A ElHawari, M.D.**, Mohamed H Emara, M.D.**, Emad F Hamed, M.D.***

Cardiology*, Tropical Medicine** and internal medicine*** Departments, Faculty of Medicine, Zagazig University, Egypt.

ABSTRACT

Background and aim: Interferon-based therapy is associated with significant side effects, including the cardiac complications; these may affect the patients' adherence to therapy and consequently the response rate. The aim of this study was to detect the types and predictors of interferon induced cardiac complications in the Egyptian hepatitis C virus infected patients treated with pegylated interferon/ribavirin combination therapy.

Patients and Methods: A total of 194, chronic HCV patients were followed up from the time of receiving treatment till 6 months after the end of treatment, to detect cardiac disorders and to determine the response status. Patients were assessed by through history taking, full clinical examination, full laboratory parameters and cardiac assessment using the standard 12 lead ECG and Transthoracic Doppler Echocardiography. Patients in the final analysis were divided into: Group A (who developed cardiac disorders) and group B (who did not develop cardiac disorders).

Results: The baseline clinical features (cardiovascular risk factors and hemodynamics) were comparable in both groups. Patients who developed cardiac disorders had higher baseline ALT level, hepatic fibrosis and histologic activity in the liver biopsy than patients without cardiac disorders (P<0.05). The confirmed cardiac complications represented 18% (n=35) and included left ventricular systolic and diastolic dysfunction, pericardial effusion, arrhythmia and myocardial ischemia. Histological activity in the liver biopsy, ejection fraction (EF) and left ventricular end diastolic dimension (LVEDD) were independent predictors for cardiovascular complications.

Conclusion: Pegylated interferon therapy of chronic HCV is associated with many types of cardiac complications, predictors of which were histological activity in the liver biopsy, EF and LVEDD.

Key words: Pegylated Interferon; Hepatitis C virus; Cardiovascular complications of interferon.

INTRODUCTION

Hepatitis C virus (HCV) infection is the most common cause of newly diagnosed chronic liver disease worldwide [1] and is the single most important cause of liver disease in Egypt [2,3], with the latest anti-HCV antibody prevalence of 14.7% [4]. Hence, it is very important that the disease be treated in its early stages, which will effectively reduce the morbidity and mortality associated with this disease [5]. The current recommended therapy for chronic HCV is the combination of pegylated interferon alpha (Peg-IFN-α) and ribavirin (RBV) that was proven to be superior to the standard interferon alpha and ribavirin [6, 7]. Peg-IFN-α based therapy is known to be associated with significant side effects that may have an impact on tolerability, compliance, ability to maintain optimal dosing regimens, and ultimately the response to therapy if dose reductions or discontinuations are required [8].

Cardiovascular effects related to interferon-alpha have been reported in 5 to 15% of patients [9]. A wide range of cardiac complications has been reported, including dilated cardiomyopathy (which mostly occurs after a prolonged time of treatment), arrhythmias, and ischemic heart disease. Most cardiotoxic effects, including cardiomyopathy are reversible following cessation of IFN-α [10]. Other less common and less dangerous side effects detected in less than 5% of the patients in non-randomized studies are: low-level conduction impairment or reversible hypertension and the exact physiopathology of this cardiotoxicity remains unknown [11].

In Egypt; only few registries are available till now, despite the overwhelming increase in the number of people infected with hepatitis C virus and on treatment with interferon. The aim of this study was to detect the types and predictors of interferon induced cardiac complications in the Egyptian HCV infected patients treated with pegylated interferon/ribavirin combination therapy.

SUBJECTS AND METHODS

Study: Prospective observational.

Subjects: This study has been carried out on 194 Egyptian HCV cases attending HCV treatment clinics in Zagazig University Hospitals, Sharkiya Governorate, Egypt. Cases included were referred to the Cardiology outpatient clinic, Zagazig University Hospitals for further assessment. All patients were candidates for treatment by Peg-IFN-α and RBV according to the modified guidelines of the National Committee for Control and Prevention of viral Hepatitis "C" in Egypt [12]. Patients with chronic hepatitis B (HBV), HBV/HCV coinfection, cirrhotic patients, auto-immune hepatitis; cardiac disease (cardiomyopathy, arrhythmias, ischemia, myocarditis, and valvular disorders), renal impairment, thyroid dysfunction, and psychiatric disorders were excluded from the study. Habitual alcohol drinkers and drug abusers were also excluded.

Patients were classified in the final analysis into two groups: group A comprised 96 patients who developed cardiac disorders and group B comprised 98 patients who did not develop cardiac disorders. Approval was obtained for performing the study from the Institutional Review Board of the Faculty of Medicine, Zagazig University, Egypt.

After giving an informed consent, all patients were subjected to the following:

1- Baseline demographic data collection regarding age, sex and associated chronic diseases. Cardiac evaluation; general examination, chest X-ray, electrocardiography (ECG) and echocardiographic (Echo) studies.

2- Baseline laboratory data, including HCV RNA level, bilirubin, ALT, AST, serum creatinine level, blood glucose (fasting and two hours postprandial), complete blood count (CBC), TSH, ANA titer < 1:20 and liver biopsy (grading of activity and staging of fibrosis was evaluated by Ishak [13] classification which classifies hepatic activity by a score from 1 to 18 and hepatic fibrosis from 1 to 6).

3- Treatment regimens: The Peg-IFN alpha was given subcutaneously around the umbilicus once per week together with RBV, using 1000 mg/day for those ≤75 kg in weight and 1200 mg/day for those >75 kg in weight.

4- Patient Monitoring: Patients were assessed at weeks 0, 1, 2 and 4 of treatment and thereafter monthly and on the development of symptoms. At each visit the followings were done:

- Laboratory tests, including: serum ALT, AST, bilirubin, creatinine, CBC. TSH was measured at regular intervals during and after treatment. Body weight and symptom checklist were recorded at each visit.

- Assessment of the response status for the combination therapy, by qualitative PCR, at week 12, week 24, week 48 and 6 months after the end of antiviral therapy to determine the sustained virological response (SVR).

- Cardiological assessment, including:

  a- Symptoms analysis: including shortness of breathing (SOB), paroxysmal nocturnal dyspnea (PND), palpitation and chest pain.

  b- Clinical examination, including blood pressure, pulse (for rate and rhythm), signs of heart failure (HF); neck veins for congestion, lower limbs for edema, fine bilateral basal crepitations or additional heart sounds (S3 or S4).

c- Standard 12 lead ECG, to document the presence of significant ST- T wave changes suggestive of ischemia; (when the resting ECG reveals ST-segment depression greater than 0.1 mV (1 mm), deep T-wave inversion and/or ST-segment elevation of 0.2 mV (2 mm) in chest leads and 0.1 mV (1 mm) in limb leads) [14] and rhythm or conduction disturbance.

d- Transthoracic Doppler Echocardiography (Echo): Conventional echo, and Doppler studies were performed for all patients using a Hewlett Pakard (SONOS 5500) echo-set using a 2.5 MHz transducer. Echo, study was obtained at rest with the subjects in the left lateral decubitus position. Two-dimensional guided M-mode (2D Echo) measurements of the following: left ventricular end diastolic dimension (LVEDD), LV end Systolic dimension (LVESD) and ejection Fraction (EF) %. Doppler study of the mitral valve flow measuring: the E-wave, A-wave and E/A ratio from the apical 4-chamber view. Evaluation of the pericardium was also done.

DEFINITIONS

Abnormal Echocardiographic parameters [15, 16]:

- Dilated left ventricle: when LVEDD >53mm in women and 59mm in men.
- Impaired LV systolic function: when EF< 55%.
- Impaired LV diastolic function: grade I when the mitral E/A ratio <1, grade II (pesudonormal when E/A > 1) discovered by Valsalva or by tissue Doppler and grade III (restrictive pattern) when E/A >2.

Cardiological assessment was performed by the cardiologist author and another independent cardiologist, both have high experience in ECHO studies to minimize the inter observer variability that may affect the readings.

Statistical Analysis: Data were collected and analyzed using SPSS (Statistical Package for the Social Sciences) version 15. Continuous variables were expressed as mean ± SD and categorical variables are expressed as percentages. Comparison of variables between the two groups was performed by the X^2 test and student's t test. Multivariate linear logistic regression analysis was used to find out the significant independent predictor/s of cardiac complications in patients on interferon therapy. A value of P < 0.05 was considered statistically significant.

RESULTS

Study participants

This study included 194 chronic HCV patients, 111 (57.2%) were males and 83 (42.8%) were females, their ages ranged from 18 to 60 years. All patients were followed up from the time of initiation of the combined antiviral therapy for six months after the end of treatment to determine the SVR for responder patients or the time of discontinuation of therapy for non responder patients. There were no dropouts from the scheduled cardiovascular assessment visits; all patients completed the study and were compliant with the regular interviews including the non responders. No cessation of therapy due to cardiac complications except one patient, who died due to massive, rapidly accumulating pericardial effusion (aspiration showed hemorrhagic massive effusion, its analysis showed that it was bloody, with neither inflammatory, viral nor bacterial affection of the pericardium and it was associated with thrombocytopenia). Patients' baseline characteristics are shown in Table 1.

Clinical, biochemical, virological and pathological features:

The two groups were comparable in their baseline clinical features (cardiovascular risk factors, hemodynamics), baseline viral load (quantitative PCR), biochemical features and the response rate, except for ALT that was significantly higher (50.94±27.547 IU/L) in

group A vs. (43.31±22.916 IU/L) in group B (p <0.05). Patients in group A had advanced hepatic fibrosis (p <0.05) and necro-inflammatory activity (p <0.001) in the liver biopsy when compared to patients in group B (Table 1).

Cardiac disorders in group A:
The reported Cardiac disorders (clinical, ECG and Echo) were in the form of: 13 patients developed SOB (3 with HF, 4 with palpitation and 3 with ST-T wave changes), 31 patients developed palpitation (17 with anemia and 3 with premature atrial contractions ``PAC``), 15 patients developed chest pain (3 with typical ischemic chest pain and ST-T wave changes in ECG and 6 with stitching pain of pericarditis with development of effusion in Echo). Echo study showed: LVEDD >53/59 mm in 18 patients by the end of the course, with early cardiomyopathic changes (EF<55%) in 3 cases (dilated cardiomyopathy) and 5 patients developed LV diastolic dysfunction (Table 2).

The Actual Cardiovascular Complications:
The actual rate of cardiovascular side effects in this study was 18% (n=35), of them 3 patients developed typical ischemic chest pain and ST-T wave changes in ECG with normal cardiac enzymes. Three cases showed premature atrial contractions (PAC). Echocardiographic parameters showed: marked left ventricular dilatation reported in 18 patients by the end of the course, with early myopathic changes and marked reduction in EF from base line in 3 cases (cardiomyopathy with development of HF, with FBBC, S3 gallop, lower limb edema and only one with congested pulsating neck veins, all of them improved with medical treatment within 6 months after the end of interferon course), 5 patients developed LV diastolic dysfunction (grade I in 3 patients and grade II in 2 patients), 6 cases developed pericardial effusion .We reported 1 case of death due to massive hemorrhagic pericardial effusion (Figure 1).

Echocardiographic parameters:
 There was no statistically significant difference between group A and group B as regard the echocardiographic parameters (LVEDD, LVESD, E/A ratio and EF) at the baseline, while there was a statistically significant difference between group A and group B as regard LVEDD, LVESD and EF after the end of therapy.
There was no statistically significant difference in echocardiographic parameters before and after therapy in group B patients.
LVEDD was significantly increased in group A after the end of therapy (48.9±2.44 vs 52.9±3.58 mm) (p<0.05), also LVESD was significantly increased in group A after the end of therapy (32.3±0.38 vs 35.7±2.49 mm) (p<0.05). These resulted in significant reduction in EF in group A from (71.33±6.13 %) at baseline to (59.61±12.53 %) after the end of therapy (p <0.05) (Table 3).

Predictors of cardiovascular complications:
Logistic regression analysis of different parameters in patients with cardiovascular complications showed that the advanced degree of histological activity in the liver biopsy, the lesser EF and the more LVEDD were independent predictors for the occurrence of cardiovascular complications (Table 4).

Table 1: Basal characteristics of both groups.

	Group A N=96	Group B N=98	P
Age (years)	44.3±7.9	43.6±6.4	NS
Systolic BP (mmHg)	127.2±14.009	130.56±13.09	NS
Diastolic BP (mmHg)	79.11±9	80.61±9.63	NS
Pulse rate(beat/minute)	76.75±10.95	74.4±11.24	NS
Sex			
Female (%)	47 (49%)	36(36.7%)	NS
Male (%)	49 (51%)	62 (63.3%)	
BMI Mean±SD	27.3±3.7	27.2±2.9	NS
Smoking (%)			
Negative	60.3%	57.9%	
Active	18.4%	31.6%	NS
X-smoker	21.1%	10.5%	
HTN (%)	13 (13.7%)	11 (11.2%)	NS
DM (%)	15 (15.6%)	18 (18.4%)	NS
AST (IU/L) Mean±SD	49.33±28.12	49.38±28.24	NS
ALT (IU/L) Mean±SD	50.94±27.547	43.31±22.916	<0.05
Hb (gm/dl) Mean±SD	14.1±1.907	14.49±1.35	NS
PLT (10^9/L) Mean±SD	186.7±58.3	185.3±54.1	NS
Liver Biopsy (Ishak):			
Activity	6.95±3.26	5.67±1.803	<0.001
Fibrosis	2.47±1.43	2.09±1.29	<0.05
Basal HCV RNA PCR (IU/mL)X10^5) Mean±SD	3.3±8.6	2.2±3.8	NS
Response Rate (%)	54 (55.1%)	61 (63.5%)	NS

HTN: hypertension, DM: diabetes mellitus, SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate, bpm: beat per minute, BMI: body mass Index, Hb: hemoglobin, PLT: platelets. PCR: Basal HCV RNA, NS: non-significant.

Table 2: Cardiac disorders in group A.

	Group A N=96
Shortness of breath	13 (13.5%)
Palpitations	31 (32.3%)
Chest pain	15 (15.6%)
HF	3 (3.1%)
ST –T wave changes	3 (3.1%)
Arrhythmias(PAC)	3 (3.1%)
LV systolic disturbances:	
- LVEDD (increase by >5mm from base line)	25(26%)
- LVEDD>53/59mm	18(19%)
- EF (decrease by>5% from baseline)	21(22%)
- EF<55%	3(3.1%)
LV diastolic dysfunction	5 (5.2%)
Pericardial effusion	6 (6.2%)

HF: heart failure, PAC: premature atrial contractions, LV: left ventricular, LVEDD: left ventricular end diastolic dimension, EF: ejection Fraction.

**Table 3: Echocardiographic parameters, in both groups before and after treatment.**

	Group A N=96	Group B N=98	P
LVEDD(mm) before treatment	48.9±2.44	48.3±0.50	NS
LVEDD(mm) after treatment	52.9±3.58	48.1±0.48	<0.05
LVESD(mm) before treatment	32.3±0.38	31.3±2.15	NS
LVESD(mm) after treatment	35.7±2.49	30.8±0.415	<0.05
EF(%) before treatment	71.33±6.13	70.85±5.32	NS
EF(%) after treatment	59.61±12.53	71.93±6.05	<0.05
E/A before treatment	1.15±0.281	1.22±0.282	NS
E/A after treatment	1.16±0.278	1.2±0.251	NS

LVESD: LV end Systolic dimension, E: peak early diastolic mitral flow, A: peak late diastolic mitral flow, NS: non-significant. Differences in the parameters before and after IFN-α therapy were assessed by the paired t-test.

Table 4: Logistic regression analysis, of the different parameters, in patients with cardiovascular complications.

Variable	B	Wald	Sig.
Age	-0.014	0.417	NS
Sex	-0.639	3.317	NS
ALT	.006	.336	NS
PCR	0.000	0.409	NS
Histological activity	.467	6.492	<0.05
Hepatic fibrosis	-.252	.626	NS
LVEDD	3.189	18.016	<0.001
LVESD	-1.401	3.404	NS
Ejection fraction	-.165	11.462	<0.001

PCR: Basal HCV RNA, LVEDD: left ventricular end diastolic dimension, LVESD: left ventricular end Systolic dimension, EF: ejection Fraction.
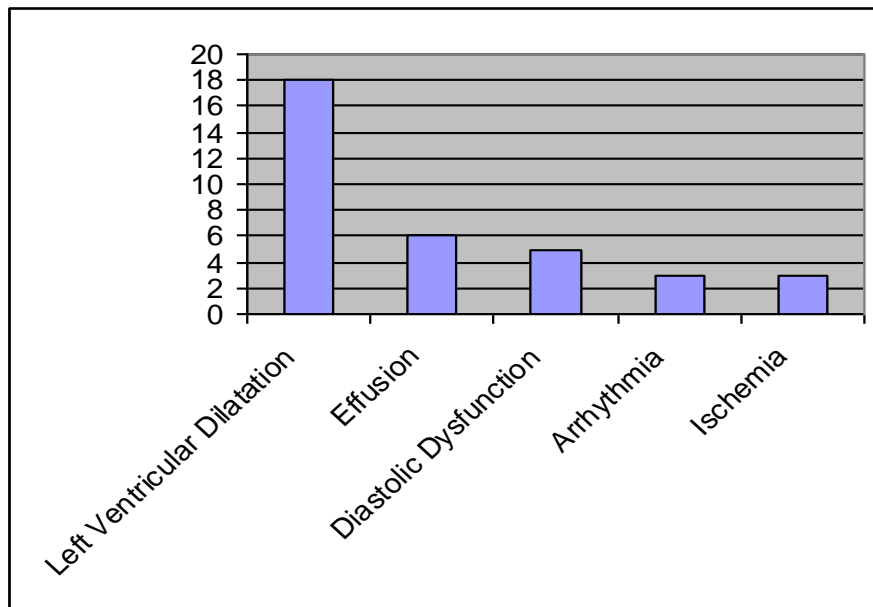
Figure 1: The reported cardiovascular complications.

DISCUSSION

Chronic HCV is being increasingly treated, and infectious disease physicians as well as young gastroenterologists are more and more incorporated in the management with interferon based therapies. Many of them are not familiar with the serious cardiovascular complications of interferon, especially in Egypt, where a nationwide HCV treatment program under surveillance of the Ministry of Health and the Health insurance conduced years ago. Consequently, many patients are treated, and the chance to develop these complications increases.

This study found that interferon based therapy is associated with various cardiovascular complications and some of them end with case fatalities, a serious concern that should raise not only physicians' but also patients' awareness about these adverse events and importance of adherence with the scheduled regular interviews.

The rate of cardiovascular complications in this study was 18%, a rate higher than the rate reported in the international [9, 11] as well as the Egyptian literature [17]. In fact, an interesting study from Egypt by Almawardy R et al., [17], assessed the myocardial toxicity of interferon in a 120 chronic HCV patients at baseline and 6 months after initiation of the combination therapy, they excluded non responders and there was a dropout of 45 patients and they reported rates of myocardial toxicity lower than the rates we reported. This can be explained by many reasons. Firstly, the aim of our study was to report all cardiovascular side effects including the asymptomatic Echo changes and not only to assess myocardial function. Secondly, the large number of patients in our cohort compared to the smaller number of patients in many other studies. Thirdly, the duration of follow up: 6 months after end of treatment in our study. This enabled us to pick up delayed cardiovascular complications of interferon even after cessation of treatment. Fourthly, cardiovascular follow up visits (multiple cardiac assessment visits). Fifthly, the rate of dropouts (the cardiovascular assessment interviews): none in our study. Furthermore, we did not exclude the non-responder patients who still at risk of developing cardiovascular complications due to

the cumulative effect of Peg-IFN-α /RBV irrespective of their response status.

Left ventricular dilatation and consequently reduction in EF were the most common cardiovascular complications reported in this study to the degree of cardiomyopathy in 3 cases. There are multiple mechanisms by which a potent activator of the immune system such as IFN could induce myocardial dysfunction and cardiomyopathy, including new or enhanced immunoglobulin production as detected by the presence of specific antibodies against myocytes in the blood of the affected patients [18] and enhanced cell mediated immunity as detected in the biopsy and autopsy [19].

Higher rates of HCV induced myocarditis and cardiomyopathies were reported from the Japanese literature [20]. It was also reported from the West and even resolution of heart failure and myocardial injury was reported in HCV patient after complete eradication [21]. These data need further confirmation in Egyptian patients and should be studied in relation to HCV genotype.

Myocardial ischemia reported in this study was not progressed to myocardial infarction, meanwhile the risk to develop this potentially fatal complication is present due to many factors associated with IFN therapy, including anemia that commonly complicate patient management both due IFN induced bone marrow suppression and RBV induced hemolytic anemia. Ischemic events may also result from the property of IFN-alpha to increase the thickness of capillary walls leading to narrowing of the luminal size as was shown in an animal model [22]. The presence of anti-INF antibody in the absence of pathologic alterations on coronary angiography, suggest that the coronary spasms were the result of an immune mechanism [22, 23]. INF has also been shown to influence the cytokine network and autonomic nervous system functions which may result in coronary vasospasm [24]. In addition, IFN- alpha has been demonstrated to yield an unfavorable lipid profile consisting of an increase in triglycerides and very low density lipoprotein (VLDL) cholesterol while high density lipoprotein (HDL) cholesterol decreased [25].

The types of arrhythmias reported in this study were of atrial origin. Interferon induced arrhythmia is not a novel finding of this study, where a 58-year old Egyptian female reported ventricular extra-systoles on top of sinus tachycardia with syncopal attacks and was overcome by IFN dose reduction [30].

Interferon may have induced local inflammation in the conduction system in response to an immune reaction, resulting in variable types of arrhythmia (ventricular or supra-ventricular) [26]. It may induce ventricular late potentials and related arrhythmias in patients with chronic active hepatitis due to the reversible electro-physiological effects of IFN [27], or cause sympathetic nervous system activation [28]. Another study suggested that the arrhythmogenic effect of the standard INF may be mediated by decreases in heart rate variability indices [29].

IFN-α is known to induce expression of various chemokines [31], that results in increased pericardial inflammation and fibrosis, leading to pericarditis and also myocarditis [32]. We reported 6 cases with pericardial effusion; one case developed tamponade and died.

In this study the occurrence of cardiovascular troubles was higher in patients with higher baseline ALT, hepatic fibrosis and hepatic histological activity. We have no data from the available literature about this association, but advanced hepatic affection reflected by these parameters may point to cardiac affection as well, added to the cardio-toxic effect of IFN and this may be another explanation for the high rate of complications reported in this study.

In conclusion, cardiovascular complications in Egyptian chronic HCV patients treated with pegylated IFN alpha are not infrequent. Patients with high baseline ALT, hepatic fibrosis and histologic activity are prone to develop these complications. So

rigorous cardiological monitoring of all patients receiving this treatment seems necessary.

Larger studies using more investigation modalities for detection of myocardial injury and further follow up of the complicated cases are recommended for longer time.

Acknowledgment: To Dr. Layla M El Maghawry, following her guidance we soundly conducted this study in its present form. We also would thank all staffs who share in the arrangement and delivery of the services to the patients.

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أنواع وعوامل التنبؤ بالمضاعفات القلبية للعلاج بالانترفيرون و الريبافيرين فى المرضى المصريين المصابين بفيروس سى المزمن

ابتسام الدسوقى¹، سها عبدالمنعم الهوارى ²، محمد حسن عمارة²، عماد فوزى حامد³

قسم القلب و الاوعية الدموية ¹ ، كلية الطب البشرى، جامعة الزقازيق، مصر

قسم الامراض المتوطنة ² ، كلية الطب البشرى، جامعة الزقازيق، مصر

قسم الباطنة العامة ³ ، كلية الطب البشرى، جامعة الزقازيق، مصر

الخلفية العلمية و هدف البحث:

ينطوى العلاج بالانترفيرون على مضاعفات كثيرة تشمل القلب، وتؤثر هذه بدورها على انتظام المريض فى العلاج و من ثم نتائجه. وقد هدفت هذه الدراسة الى تحديد انواع وعوامل التنبؤ بالمضاعفات القلبية للعلاج بالانترفيرون و الريبافيرين فى المرضى المصريين المصابين بفيروس سى المزمن.

المرضى و طرق البحث:

شمل هذا البحث على مائه واربعة وتسعين مريضا تم تتبعهم من بدء العلاج و حتى ٦ أشهر بعد انتهاءه لتحديد معدلات الاستجابة و الاثار الجانبية. و تم تقييم المرضى بالفحص الاكلينيكى، الفحص المعملى، رسم القلب ، اشعة الاكو على القلب. تم تقسيم المرضى الى مجموعة أ (لديهم مضاعفات قلبية) و مجموعة ب (ليس لديهم مضاعفات قلبية).

النتائج:

تشابهت المجموعتان فى الصفات الاكلينيكة، مرضى المجموعة (أ) كان لديهم مستويات اعلى من انزيم الكبد، درجة التليف و النشاط النسيجى عنه فى المجموعة (ب). المضاعفات المؤكدة على القلب فى هذا البحث مثلت 18% و شملت اضطراب وظائف البطين الأيسر ، إنصباب التامور ، ،عدم إنتظام ضربات القلب ، ونقص تروية عضلة القلب. عوامل التنبؤ بالمضاعفات القلبية للعلاج بالانترفيرون و الريبافيرين كانت درجة النشاط النسيجى فى عينة الكبد، نسبة الجزء المقذوف من البطين و مقاس البطين الايسر فى نهاية دورة الانبساط.

الخلاصة

العلاج بالانترفيرون و الريبافيرين ينطوى على مضاعفات قلبية كثيرة. عوامل التنبؤ بالمضاعفات القلبية للعلاج بالانترفيرون و الريبافيرين كانت درجة النشاط النسيجى فى عينة الكبد، نسبة الجزء المقذوف من البطين ومقاس البطين الايسر فى نهاية دورة الانبساط.