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Original Article

Ribavirin Induced Anemia among Patients with Hepatitis-C at Tertiary Care Hospital.

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Abstract

Introduction: Hepatitis C is among one of the major global health issues; which may cause chronic liver disease, end stage liver disease, and hepatocellular carcinoma; subsequently requiring liver transplant. For HCV, standard treatment is a combination therapy of ribavirin and interferon for six months. Ribavirin fostered hemolysis is a major treatment-associated adverse effect.
Objective: To assess ribavirin induced anemia among Hepatitis C patients visiting Civil Hospital, Karachi (CHK).
Methodology: This hospital-based cross-sectional study was conducted from October 2017 to January 2018. 106 Hepatitis C patients; through non-probability convenient sampling technique; visiting CHK, a public sector tertiary care hospital were enrolled.
Results: Among106 patients, 53 (50.0%) were males and 53 (50.0%) were females. Mean ±SD age was 37.05 ±10.793. Mean ±SD duration of ribavirin use was 3.03 ±1.523 months. Around 16.0% had ribavirin dose reduction. All of them experienced weakness, fatigue and light-headedness, 59.4% developed microcytic hypochromic anemia, 23.6% had severe anemia. Mean ±SD hemoglobin (g/dL) level before the onset of treatment was 12.78 ±1.555. Mean hemoglobin level during treatment was 10.72g/dL. Mean reduction in hemoglobin levels was 2.07g/dL. The reduction in hemoglobin levels and the duration of therapy were correlated (p-value <0.05). The severity of anemia was related to age of the patients (p-value <0.05) but not with gender and morphology of red blood cell.
Conclusion: Ribavirin induces anemia, its severity is related to the duration of ribavirin therapy and initial hemoglobin levels. It is sometime severe enough to warrant dose reduction and consequently suboptimal dose of ribavirin affect efficacy.

Key Words: Hepatitis C, Ribavirin, Microcytic Hypochromic Anemia.

Introduction:

Hepatitis C Virus (HCV) infection is among one of the major global health issues and significant public health burden; when chronic may cause CLD (chronic liver disease), end stage liver disease (ESLD) and hepatocellular carcinoma, leading to significant morbidity and mortality, subsequently requiring liver transplant.[1,2] Numerous treatment strategies are available and a few are still in progress that adjuvant oral therapy along with optimum efficacy (>90% cure rates), brief treatment duration (3-4 months), few contraindications and side effects comparable with treatment options available currently.[3]As no vaccine is available, primary prevention including safer blood transfusion and injection via sterile needles should always observed. For HCV infection, standard treatment is a combination therapy of ribavirin and interferon for six months.[4] Ribavirin fostered hemolysis is an important treatment-associated adverse effect, affecting the quality of life.[5,6] Drug interaction, adverse effects

and cost effectiveness are continuously challenging this regimen.[2] Undoubtedly ribavirin plus interferon-based therapies distinctly improves sustained viral response rates. Nearly every patient suffered anemia.[7]According to a study, 39% of patients developed severe anemia[8], whose management required ribavirin dose adjustment and epoetin alfa therapy during ribavirin and interferon combination therapy.[9] Another study suggested that when the dose of ribavirin was modified, the severity of anemia improved by 50%.[1] According to an American study, there was an association between the plasma ribavirin concentration and anemia.[11]

This study was conducted to assess ribavirin induced anemia among Hepatitis C patients visiting Civil Hospital Karachi.

Methodology:

This hospital-based, cross-sectional study prospective study was conducted between October 2017 to January 2018 at outpatient's department of Civil Hospital Karachi. The diagnosed patients of Hepatitis C, taking prescribed combination therapy of ribavirin and interferon for more than 15 days but less than 6 months, aged 15-60 years of either gender having report of complete blood count done prior to the initiation of the régime with them were selected using non-probability convenience sampling were chosen. Informed written was sought from participants and finally 106 patients were selected for the study. All those who refused to participate, had other forms of hepatitis, were diagnosed but not investigated for genotype, in whom Ribavirin was contraindicated (hemoglobinopathies, etc.); those who completed six months ribavirin treatment, patients <15 years or >60 years; those who didn't have CBC report showing previous and current hemoglobin levels, had decompensated HCV-CLD (ascites, splenomegaly or portal hypertension) were excluded from the study.

A self-administered closed ended questionnaire used to collect information. This includes patients' demographic data, duration of diagnosis of hepatitis, duration of ribavirin therapy, frequency and dosage of ribavirin, any change in the dosage of ribavirin therapy, alcohol intake, symptoms of anemia (shortness of breath, light-headedness, weakness and fatigue, pale skin). Patients were inquired for their CBC reports for the hemoglobin levels before starting the treatment, current hemoglobin levels and RBC morphology. All the participants were briefed regarding the objectives of this study and assured for their confidentiality and anonymity.

The data collected was analyzed using Statistical Package for Social Sciences (SPSS) version 16.0. Frequency and percentages were calculated. Descriptive statistics were calculated for continuous data as mean and standard deviation. Chi-Square test was applied to find the association of socio demographic variables with difference in hemoglobin levels during treatment, duration of ribavirin used with difference in hemoglobin levels during treatment. P value less than 0.05 was considered statistically significant.

Results:

A total of 106 HCV patients were included in the study; among them 53 (50.0%) were males and 53 (50.0%) were females. Five participants (4.7%) were of less than 20 years, 53 (50.0%) of 20-40 years ago, while 48 (45.3%) were 40-60 years old. Regarding the duration of diagnosis of Hepatitis C, 46 patients (43.4%) had Hepatitis C for less than 1 year, 32 (30.2%) for 1-2 years, 19 (17.9%) for 2-3 years, 7 (6.6%) for 3-4 years, while 2 (1.9%) were living with Hepatitis C for 4-5 years. Duration of ribavirin use was 1 month in 21 patients (19.8%), 24 (22.6%) for two months, 20 (18.9%) for three months, 16 (15.1%) for four months, 21(19.8%) for five months, while 4 (3.8%) were taking ribavirin for six months along with interferon. Among all 17 patients (16.0%) underwent dose modification because of worsening anemia.

Weakness, fatigue and light-headedness were reported by all the patients (100%), breathlessness by 76 (71.7%), paleness of skin color by 42 (39.6%); while 63 (59.4%) developed microcytic hypochromic anemia as indicated by their CBC [Table I].

While being on ribavirin therapy, 25/106 respondents (23.6%) had severe anemia (hemoglobin <10g/dL). Mean ±SD duration of ribavirin use was 3.03 ±1.523 with the range 1-6 months. Mean ±SD hemoglobin level before the onset of treatment was 12.78 ±1.555. Mean hemoglobin level during treatment was 10.72g/dL. Mean reduction in hemoglobin levels was 2.07g/d [Table II]. The reduction in Hemoglobin levels and the duration of therapy were correlated (p-value <0.05) [Table III, Figure I].

There was statistically significant relationship between duration of ribavirin therapy and reduction in hemoglobin levels (p-value 0.000). There was no significant relationship between gender and difference in hemoglobin levels during therapy (p-value 0.697). The reduction in hemoglobin level had significant relationship with age (p-value 0.013). Hemoglobin reduction and ribavirin dose reduction were related (p-value 0.000). The duration of ribavirin used, and microcytic hypochromic anemia were not significantly related (p-value 0.576). Severity of anemia with initial hemoglobin levels, current hemoglobin levels with RBC morphology were related and statistically significant (p-value 0.000).

Table I: Frequency and Percentage of Clinical Data (Hemoglobin According to CBC Report)

Variables		Frequency	Percent
RBC Morphology	Normocytic Normochromic	43/106	40.6%
	Microcytic Hypochromic	63/106	59.4%
Difference in Hemoglobin Levels During Treatment	1g/dL	40/106	37.7%
	2g/dL	31/106	29.2%
	3g/dL	23/106	21.7%
	4g/dL	9/106	8.5%
	5g/dL	3/106	2.8%
Hemoglobin Level Before Onset of Treatment	10-11g/dL	4/106	3.8%
	11-12g/dL	21/106	19.8%
	12-13g/dL	26/106	24.5%
	13-14g/dL	18/106	17.0%
	14-15g/dL	24/106	22.6%

	15-16g/dL 16-17g/dL 17-18g/dL	7/106 5/106 1/106	6.6% 4.7% 0.9%
Hemoglobin Levels During Treatment	<10g/dL >10g/dL	25/106 81/106	23.6% 76.4%

Table II: Descriptive Statistics of Clinical Data (Mean and SD)

Variables	Mean	±SD
Difference in Hemoglobin Levels During Treatment (g/dL)	2.0943	1.09134
Hemoglobin Before Start of Treatment (g/dL)	12.7830	1.55536
Current Hemoglobin levels (g/dL)	10.7264	1.72673
Duration of Diagnosis of Hepatitis C (years)	1.9340	1.02603
How Long Ribavirin use (months)	3.0377	1.52393
Age (years)	37.0566	10.79315

Table III: Difference in hemoglobin level with the duration of therapy (using chi-square test)

Duration of Ribavirin use	Difference in Hemoglobin levels				
	1g/dL	2g/dL	3g/dL	4g/dL	5g/dL
1 month	20	01	00	00	00
2 months	13	08	03	00	00
3 months	06	12	02	00	00
4 months	00	07	07	02	00
5 months	01	02	11	05	02
6 months	00	01	00	02	01

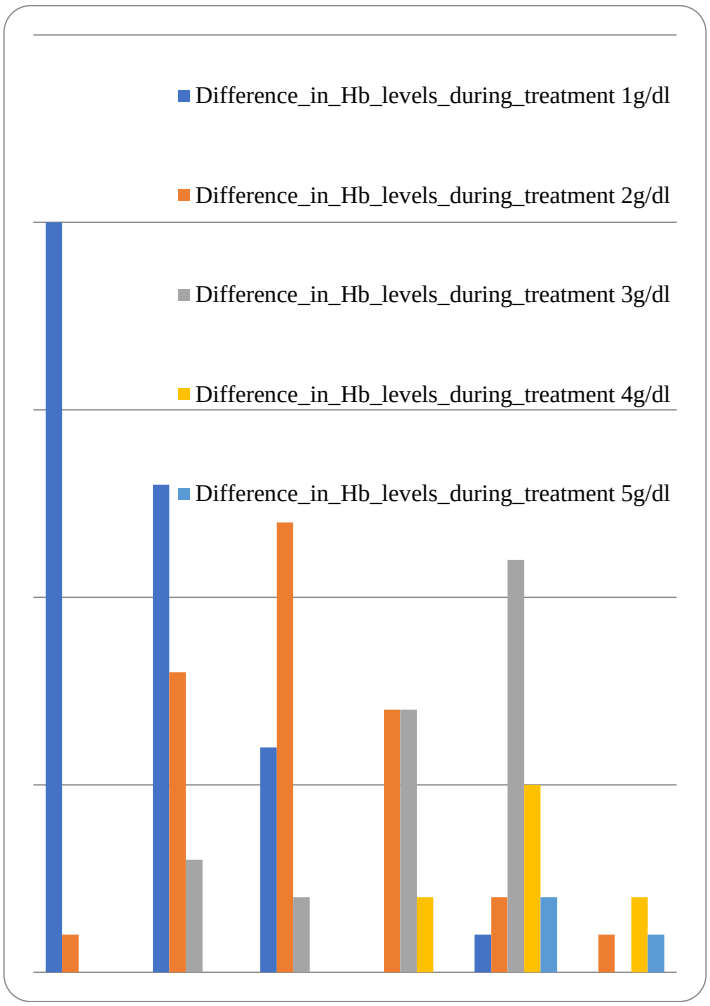

Figure I: Duration of Therapy & Difference in Hemoglobin Levels (x-axis representing the duration of therapy, whereas y-axis representing number of patients with their respective difference in hemoglobin levels as mentioned with specified colors in the graph).

Discussion:

The treatment adequacy of HCV relies upon the compliance to the optimum dose and duration of therapy. The treatment efficacy reduces whenever there comes the factor of non-compliance/dose modification/drug withdrawal due to rapidly worsening adverse effects of combination therapy. Anemia is one of them as ribavirin induces hemolysis and erythropoiesis being directly inhibited by interferon.[12] The reduction in hemoglobin level and the resultant anemia varies among individuals depending upon the duration of therapy.[13,14] Some patients remains asymptomatic until marked reduction in hemoglobin levels.

According to this study, most of the patients (50.0%) were 20-40 years of age. Majority had Hepatitis for less than 1 year (43.4%). It was observed that 23.6% had severe anemia, maximum hemoglobin reduction was in second month of therapy (22.6%) with mean maximum decrease of 1.583g/dL and 16.0% had ribavirin dose reduction which contrasts with the result of a national study showing maximum hemoglobin reduction was during 1st month of

therapy with the mean maximum decrease of 2.05g/dL[12]. Another study from Italy also showed contrasting results with marked reduction in hemoglobin was during 1st month.[5] It is also supported by a study conducted in Canada and Netherland.[15]Another study shows 13% patients needed dose modification due to worsening anemia.[16,17]

During therapy, hemoglobin levels kept on decreasing throughout six months which is contrary to a study showing hemoglobin reduction till four months and then improved.[18]

According to our study, weakness, fatigue and light-headedness were experienced by all patients, breathlessness by 71.7%, and 39.6% had paleness of skin color due to increasing severity of anemia and decreasing hemoglobin levels. Whereas, 59.4% patients, even had microcytic hypochromic anemia evident by their complete blood picture. Reduction in hemoglobin levels is not influenced by gender but with age which is in contrast to another study that shows male gender comparatively has marked difference in hemoglobin levels.[19]Another study depicts that severity of anemia is related with female gender, body weight and old age.[8] While a Japanese study manifested body weight statistically related with reduction in hemoglobin levels.[20]

Conclusion:

Ribavirin induces anemia, its severity is related to the duration of ribavirin therapy and initial hemoglobin levels. It is sometime severe enough to warrant dose reduction and consequently suboptimal dose of ribavirin affect efficacy

Recommendations:

Further studies are recommended to obtain data not only from other public sector tertiary care hospitals but also from private sector.

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