Original Article

RIBAVIRIN INDUCED ANEMIA: A CROSS SECTIONAL STUDY AMONG PATIENTS WITH HEPATITIS C, VISITING OUT PATIENT DEPARTMENT OF A MAJOR PUBLIC SECTOR TERTIARY CARE HOSPITAL, KARACHI, PAKISTAN.**Zulfiqar Ali Shaikh¹, Javeria Shamim², Kelash Nankani³**¹Professor, Community Medicine, Dow Medical College/DUHS, Karachi²Final Year Student, Dow Medical College/DUHS, Karachi³Professor, Physiology, Dow Medical College/DUHS, Karachi**Correspondence:** Zulfiqar Ali Shaikh, Email: drzulfiqarshaikh@gmail.com**Abstract**

Background: 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. Our study aimed to assess ribavirin induced anemia among Hepatitis C patients visiting Civil Hospital, Karachi.

Methods: A hospital-based cross-sectional study which included 106 Hepatitis C patients, of 15-60 years' age, visiting CHK, a public sector tertiary care hospital, from October 2017 to January 2018 by using non-probability convenient sampling technique.

Results: Total 106 patients participated, 53 (50.0%) were males and 53 (50.0%) were females. Mean ($\pm$ SD) age was 37.05 ($\pm$ 10.793). Mean ($\pm$ SD) duration of ribavirin use was 3.03 ($\pm$ 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 ($\pm$ SD) hemoglobin level before the onset of treatment was 12.78 ($\pm$ 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 RBC morphology.

Conclusion: Ribavirin induces anemia. The duration of ribavirin therapy and initial hemoglobin levels were related to the severity of anemia, significant enough to cause dose modification and subsequently suboptimal levels affecting efficacy. In return hemoglobin reduction, dose modification and age of the patient were also related.

Keywords: Hepatitis C, ribavirin, microcytic hypochromic anemia.

Introduction

Hepatitis C Virus (HCV) is among one of the major global health issues and significant public health burden, which when chronic, is responsible for causing CLD (chronic liver disease), ESLD (end stage liver disease) 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 adjust 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 Primary prevention, without a potent vaccine, is safer blood transfusion and injection via sterile needles. In people with advanced liver disease, strategy for secondary prevention is screening for timely detection of infection and termination of alcohol consumption.¹ 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 anemia⁸, whose management required ribavirin dose adjustment and epoetin 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 was a hospital-based, cross-sectional study. Data were collected from the diagnosed patients of Hepatitis C, visiting Hepatitis OPD of Civil Hospital Karachi, a public sector tertiary care hospital, prescribed a combination therapy of Ribavirin and interferon for six months, chosen according to the inclusion criteria of this study. The study was conducted from October 2017 to January 2018. The Sample size was decided to be 106 using non-probability convenient sampling technique. We included those patients who visited Hepatitis OPD of CHK, 15-60 years of age, willing to participate after taking informed consent, already diagnosed with Hepatitis C and prescribed with ribavirin plus interferon, taking this therapy for >15 days but <6 months, had a CBC reports with them before starting the treatment and another CBC report showing current hemoglobin levels and morphology were included. All those were excluded 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 and RBC morphology or had decompensated HCV-CLD (ascites, splenomegaly or portal hypertension).

The questionnaire included the 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. A self-administered, closed-ended questionnaire was used. All the participants were briefed regarding the objectives of this study and assured for their confidentiality and anonymity.

The data were analyzed by 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 use 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 age, 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.

For the ribavirin use, 21 patients (19.8%) were taking it for one month, 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. Of them 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 1).

Table 1: Frequency and Percentage of Clinical Data (hemoglobin according to CBC report)

Variables		Frequency	Percent (%)
RBC morphology	Normocytic	43/106	40.6%
	Normochromic		59.4%
	Microcytic	63/106	
	Hypochromic		
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 the 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	7/106	6.6%
	16-17g/dL	5/106	4.7%
	17-18g/dL	1/106	0.9%
Hemoglobin levels during treatment	<10g/dL	25/106	23.6%
	>10g/dL	81/106	76.4%

While being on ribavirin therapy, 25/106 respondents (23.6%) had severe anemia (hemoglobin <10g/dL). Mean ($\pm$ SD) duration of ribavirin use was 3.03 ($\pm$ 1.523) with the range 1-6 months. Mean ($\pm$ SD) hemoglobin level before the onset of treatment was 12.78 ($\pm$ 1.555). Mean hemoglobin level during treatment was 10.72g/dL. Mean reduction in hemoglobin levels was 2.07g/d (table 2).

Table 2: Descriptive statistics of clinical data (mean and standard deviation)

Variables	Mean	Standard Deviation
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

The reduction in Hemoglobin levels and the duration of therapy were correlated (p-value <0.05) (table 3, figure 1)

Table 3: 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 1: 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)

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 use 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).

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 remained 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 was in contrast to another Pakistani study showing maximum hemoglobin reduction was in first month of therapy with the mean maximum decrease of 2.05g/dL¹². Also contrary to an Italian study showing marked reduction in hemoglobin was during first month.⁵ It was also supported by a study conducted in Canada and Netherland.¹⁵ Another study showed 13% patients needed dose modification due to worsening anemia.^{16,17}

During therapy, hemoglobin levels kept on decreasing throughout six months which was 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 of the 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 was not influenced by gender but with age which was in contrast to another study that showed male gender comparatively had marked difference in hemoglobin levels.¹⁹

Another study depicted severity of anemia was 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. The duration of ribavirin therapy and initial hemoglobin levels were related to the severity of anemia, significant enough to cause dose modification and subsequently suboptimal levels affecting efficacy. In return hemoglobin reduction and dose modification were also related. The severity of anemia was also related to age of the patients but not with gender.

Recommendations

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

Acknowledgment

We are grateful to our study participants.

Source of funding

None

Conflicts of interest

There were no conflicts of interest.

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