ORIGINAL ARTICLE

Ribavirin Induced Hemolytic Anemia In Patients Infected With Chronic Hepatitis C Virus

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[1]Conception, synthesis, planning of research and writing of manuscript
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ABSTRACT

Objective: The objective of this study was to determine the ribavirin-induced hemolytic anemia in patients infected by chronic hepatitis c virus.

Study Design: Descriptive Case series study.

Place and Duration: Gastroenterology Unit, Isra University Hospital, Hyderabad from 15-10-2014 to 15-04-2015.

Methodology: Total 102 patients were included. Complete and relevant gastrointestinal and systemic examination was performed with special emphasis on anemia and its manifestations. Every patient was tested with hepatitis C antibodies, (HCV RNA PCR positive), pre-treatment hemoglobin levels, and at twelve weeks, twenty-four weeks, and at forty-eight weeks of ribavirin treatment and documented on structured questionnaire. The laboratory data were also collected by the researcher and pathologist. Hemoglobin levels were checked before and after start of ribavirin at 12 weeks 24, and 48 weeks.

Results: The patient's mean age was 41.68±11.91 years. 41.18% of patients diagnosed with hemolytic anemia. A significant proportion of hemolytic anemia was observed in middle-aged group (34–48years), P–value 0.033. Mean reduction of hemoglobin levels were observed after 12 weeks. No significant association of hemoglobin levels was observed, in those who received ribavirin for 12 and 48 weeks P value 0.295.

Conclusion: Noticeable frequency of hemolytic anemia observed among HCV patients treated with ribavirin.

Key Words: Chronic hepatitis C virus, Ribavirin, Hemolytic Anemia

Introduction

Ribavirin is an antiviral drug that blocks messenger RNA and prevents the viral replication. It is a guanosine analogue having little antiviral activity when used alone.[1] It is widely used these days in a treatment of hepatitis C. Effectiveness of treatment increases when used in combination with interferon.[1;2] Exposure to Ribavirin is important in maximizing response to hepatitis C virus (HCV).[3] Chronic hepatitis C infection is associated with substantial morbidity and mortality. Improved treatment regimens including a combination of interferon and Ribavirin have increased sustained virological response rates (SVR) but are often associated with adverse reactions.[4] The combination therapy is not without harmful effects, the major side effect being hemolytic anemia.[5] The mechanism by which Ribavirin causes hemolytic anemia is not well established. However, it is proposed that Ribavirin after uptake into the cells is phosphorylated and it must be dephosphorylated for elimination from the cells. However red cells lack dephosphorylating enzymes Ribavirin accumulates in cells causing hemolytic anemia.[6] Hemolytic anemia is most frequently encountered and has a significant effect on morbidity and mortality of patients and it is prevalence is 10% in patients taking Ribavirin.[7;8] Hemolytic

concentration before the start of treatment could be a significant factor in Ribavirin induced hemolytic anemia.[7] However this is dose dependent and is reversible after stoppage of treatment or dose reduction. It is especially of concern as it is more problematic in patients with hepatitis c infection and associated with co-morbidities like renal and cardiovascular disorders.[8;9] Hemoglobin concentration which is used as a marker for evaluation of the severity of hemolytic anemia is done routinely and at 2 and 4 weeks after the start of treatment.[10] Ribavirin-induced hemolytic anemia could be managed with high doses of erythropoietin with close monitoring of hemoglobin concentration.[6;7] It is costly to measure serum Ribavirin concentration and they are not immediately available. So, it is not feasible for every patient to have these assays. But the measurement of hemoglobin concentration is simple, quick, and inexpensive.[6] So it is vital to have a clear idea of this side-effect in patients taking Ribavirin. As Ribavirin is frequently used in our setup in patients with hepatitis C so we would have a clear idea of its known important side effect i.e. hemolytic anemia. If it is high then clinicians must keep in mind the serious side effects as it may contribute to misery of already anemic patients due to hepatitis C, so we will do inexpensive easily available hemoglobin level, peripheral film and reticulocyte count, so that appropriate measures should be taken either to decrease the dose of Ribavirin or stop if possible.

Methodology

This descriptive case series study was carried out at Gastroenterology department of Isra University Hospital, Hyderabad after approval of hospital ethical committee. Study duration was 6 months from 15-10-2014 to 15-04-2015. All HCV positive patients receiving ribavirin therapy for 12 weeks or more of either sex and age ≥20 years were included in the study. All the patients receiving ribavirin other than HCV, already diagnose cases of hemolytic anemia due to other drugs, hemolytic anemia related to other diagnosed systemic diseases like renal, hematological, gastrointestinal, cardiovascular, or respiratory, all the patients with congenital hemolytic anemia were excluded from study. Detailed medical history regarding age, gender, and duration of drug intake was taken from each study subject. Complete and relevant gastrointestinal and systemic examination was performed with special emphasis on anemia and its manifestations. Every patient was tested with hepatitis C antibodies, (HCV RNA PCR positive), pre-treatment hemoglobin levels, and at twelve weeks, twenty-four weeks, and at forty-eight weeks of ribavirin treatment and documented on a structured questionnaire. Complete examination was conducted by the researcher himself under the supervision of consultant gastroenterologist. The laboratory data were also collected by the researcher and pathologist. Hemoglobin levels were checked before start and after start of ribavirin treatment at 12 weeks, 24 weeks and 48 weeks. All the data was recorded in the proforma.

Data Analysis: The data was analyzed by (SPSS 16). The descriptive frequencies and percentages were computed for qualitative variables such as gender, socio-economic status, education level, and duration of ribavirin therapy (weeks). Mean and standard deviation was calculated for quantitative variables such as age and hemoglobin levels. Chi-square test was applied to see the effects of age and duration of ribavirin therapy. P-value <0.05 was considered as significant.

Results

A total of 102 cases were selected for the study. Mean age of patients was 41.68±11.91 years mostly 44(43.13%) patients were found with age group of 34-48 years among all the cases male were in majority 52.94% as compared to female participants 47.06%. Most of the patients 65.69% were illiterate, primary level educated cases were 17.65%, matric passed were 8.82% and only 7.84% patients were graduate. According to the socioeconomic status majority of the cases 61(59.80%) were found with poor socio-economic status, 30(29.41%) patients having middle socioeconomic status while only 11(10.78%) patients were with upper socioeconomic status. Mean haemoglobin level was 13.45±1.63 and mean Hematocrit Levels was found 02.88±1.51. Table No I.

Haemolytic anemia gradually increases after 12 weeks of ribavirin treatment in HCV positive patients. We found most of the patients 67.64% were with treatment duration of 12 weeks followed by 21.56% patients having

treatment duration 24 weeks, while 10.78% patients had anti HCV treatment duration was 48 weeks. Figure 1

Table I: Demographic characteristics of patients (n = 102)	
Demographic characteristics	**No. of patients/(%)**
Age groups	
18-33 years	26(25.49%)
34-48 years	44(43.13%)
49-63 years	32(31.38%)
Gender	
Male	54(52.94%)
Female	48(47.06%)
Level of education	
Illiterate	67(65.69%)
Primary	18(17.65%)
Matric	09(08.82%)
Graduate	08(07.84%)
Socioeconomic status	
Poor	61(59.80%)
Middle	30(29.41%)
Upper	11(10.78%)
Age (mean±SD)	41.68±11.91 years
Hb levels (pre-treatment) (mean±SD)	13.45±1.63
Hematocrit Levels (mean±SD)	02.88±1.51

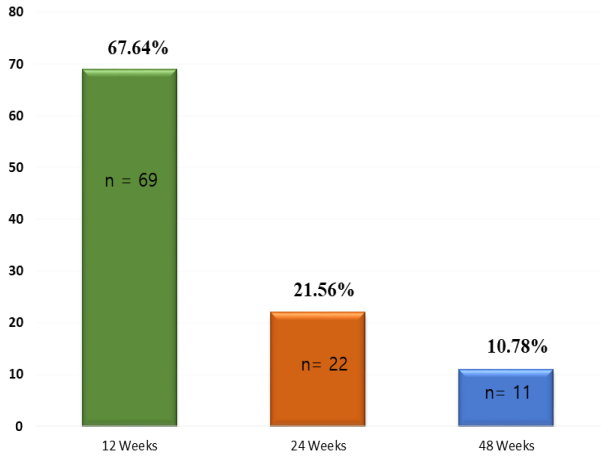

Figure 1. Duration of Ribavirin Therapy at Three Different Levels of the Study Participants (n=102)

The main cause of this study was to find out the frequency of hemolytic anemia in those patients who were suffering from chronic hepatitis C virus infection and receiving treatment with ribavirin. Out of 102 HCV positive ribavirin receiving patients, we observed a total 42 (41.18%) patients diagnosed for hemolytic anemia. Figure 2

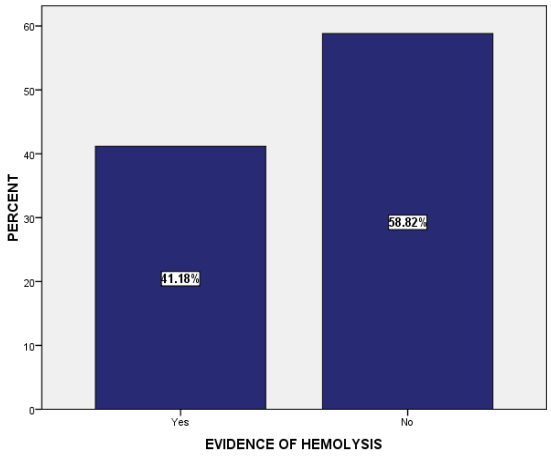

Figure 2. Percentage of HCV Patients Found to have Ribavirin Induced Hemolytic Anemia (n=102)

In most of the 18 cases out of 44, middle age group (34–48 years) was age group was observed significantly associated with hemolytic anemia and among them after receiving treatment for 48 weeks with ribavirin, 18 out of 34 patients having age group of 49 – 63 years were found haemolytic anemia, while haemolytic anemia was found in very few younger cases as; 6 out of 26 with age group of 18-33 years. p-value 0.038. Table II

Table II: Comparison of Age Groups in Patients with Ribavirin Induced Hemolytic Anemia (n = 102)			
Age Groups - Years	Hemolytic anemia		P - Value
	Yes	No	
18 – 33	6	20	0.038*
34 – 48	18	26	
49 – 63	18	14	
Total	42	60	

*P-value <0.05 was taken as significant

Cross-tabulation was performed to observe the association between hemoglobin levels among hemolytic anemic patients. An insignificant association of hemoglobin levels was observed those who received ribavirin for 12 and 48 weeks (P-value 0.295) Table III

Table III: Comparison of Ribavirin Duration in Patients with Ribavirin Induced Hemolytic Anemia (n= 102)			
Ribavirin Therapy (Weeks)	**Hemolytic anemia**		**P - Value**
	Yes	**No**	
12 weeks	32	37	0.295
24 weeks	07	15	
48 weeks	03	08	
Total	42	60	

*P-value <0.05 was taken as significant

Discussion

Worldwide most commonly use combination antiviral therapy is ribavirin and interferon for the treatment of chronic hepatitis C virus infection. It has been attributed that use of ribavirin cause hemolytic anemia which is considered to be the major but reversible side effect this antiviral therapy. Ribavirin causes decrease in the level of adenosine triphosphate and in turn hexose monophosphate shunt (HMS) increases.[11] In our study mean and SD of age was 41.68 ± 11.91 years and among all of the cases male percentage was noticed high compared to female ones 52.94% vs. 47.06%, respectively. This favors that most of the study population based on younger population. Study conducted at France shows older population was commonly encountered in their study but percentage of male cases observed highly frequent (62%) as in our study [12]. In another study conducted in Rawalpindi male cases were commonly observed.[13] Approximately all patients who were receiving pegylated interferon in combination with ribavirin develop one or more than one side effects during their period of treatment. These adverse effects can be mild to severe and may force the patients to stop the treatment[14]. The most common side effect associated with this treatment is hemolytic anemia and also the major reason to stop the treatment. Other side effects include nausea, dyspnea, muscular pain, back pain, and other skin problems.[15] Out of 102 HCV positive ribavirin receiving patients, we observed a total 42 (41.18%) patients with hemolytic anemia. On other hand in a meta-analysis conducted by Druyst E et al. 2012 has shown the prevalence of Anemia (11%), associated with 4 week treatment of ribavirin.[16] A decline in hemoglobin lower than 10 gm/dL noticed in roughly 20% and lower than 8.5 gm/dL in around 5% of patients who were on ribavirin due to CHC virus. In a study reported that Hemoglobin decreased at least 3gm/dL in 54% cases and 5gm/dL or more in 10% of male patients and 7% if female patients[17], representing a considerable anemia in a significant proportion of patients. A systemic literature also shows that use of combination therapy leads to decrease in >100gm/l hemoglobin level in around 7-9% of the total study subjects.[18] In our study this percentage of hemolytic anemia among total study participants is slightly higher. This could be due to late presentation of HCV patients and treatment with higher doses of ribavirin which leads to increase in the chances of hemolytic anemia. When increase in the dose of ribavirin of around 5 uM to 15 uM, the total decrease in hemoglobin noticed from 2gm/dl to around 5 gm/dl[19]. In our study level of hemoglobin decreased around 3-4gm/dl as compared to before treatment measured hemoglobin levels and after 48 weeks of ribavirin treatment. Our findings are in favor with study conducted by Gentile I et al. 2005.[20] Even though anemia unfavorably impacts patient's well-being, current examination of data of the clinical trials point out that individuals who experience the significant hemoglobin decrease more likely to eliminate virus. Sulkowski et al.[21] retrospectively analyzed 3023 cases having HCV genotype 1 incorporated in the multicenter trial and establish that experienced individuals fall in hemoglobin levels of >3 gm/dL had significant high SVR rate of 43.7% vs. 29.9% as compare to persons who had a smaller amount decreased in hemoglobin. Another study conducted on 133 patients those were treated for chronic hepatitis C virus infection with either interferon-a or pegylated interferon, with or without ribavirin, patients who were on combination therapy showed Hb decline of 2–3 gm/dL within the first 4 weeks of therapy as compare to those who were receiving monotherapy with interferon they only had mild decline in hemoglobin concentration. Study conducted in Lahore by Khalid SR, whose study also confirm our observation that use of ribavirin in HCV positive patients causes decline in hemoglobin 2gm/dl at the end of treatment.[22] The reason behind increase in the hemolysis could be due to decrease in the pre-treatment platelet level, use of Alfa-interferon dose along with ribavirin and the genotype of the chronic HCV infection. On the other hand, previous literature also suggest that use of pentoxifylline and vitamin E along with ribavirin and interferon can reduce the risk of drug-induced hemolysis and also improve compliance and sustained virological response in chronic hepatitis C infected patients.[23] In a clinical setting, a variety of threat have been recognized exposing subjects more vulnerable to ribavirin-induced anemia, and clinical studies have time after time verified advanced risk for ribavirin-induced anemia in women and patients with >50 years of age. One way to take full advantage of response of the treatment thus is to elevate ribavirin introduction to concentrations just below

wherever anemia becomes unbearable. The 2nd way is to the additional combination therapy with the growth hormone-like erythropoietin, which elevate the red blood cells production (erythrocytes) and compensate for the anemia induced by ribavirin-induced.[24] Study conducted by Oze T et al. 2008 on 482 HCV infection positive patients who were receiving ribavirin shows that older age group is more commonly (21%) diagnosed for ribavirin-induced hemolytic anemia as compare to younger or middle age group patients (9%). But in our study, we have observed high percentage of patients with hemolytic anemia in middle-aged group patients (45.23%) including both male and female cases. To prevent from these side effect patients are advised to reduce the dose of ribavirin. On the other hand, recent studies have demonstrated that reaction to therapy is powerfully predisposed by adherence to most favorable doses of interferon and particularly ribavirin. Therefore, recent researchers and clinicians are now focusing of use of growth factors such as filgrastim and erythropoietin to encourage bone marrow production of erythrocytes and leukocytes to permit patients to obtain the best possible doses of interferon and ribavirin.[25]

Conclusion

Noticeable frequency of hemolytic anemia observed among HCV patients, treated with ribavirin. Frequency of male cases observed more frequent than female cases. This frequency observed in those patients who belongs to middle-aged group.

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