HEPATITIS RESEARCH

Folic Acid Supplementation Does Not Prevent Ribavirin-Induced Anemia

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Treatment of chronic hepatitis C consists of inteferon plus ribavirin. The major adverse effect of ribavirin is hemolytic anemia, a complication that limits therapy. Folic acid supplementation is used to improve erythropoiesis in chronic hemolytic anemia. The aim of this study was to evaluate the effectiveness of folic acid supplementation in the prevention of ribavirin-induced anemia in patients being treated for hepatitis C. Twenty one patients enrolled in treatment protocols for hepatitis C received folic acid 1 mg daily and 22 did not. Groups were similar in age, gender, ribavirin dose and baseline hemoglobin. Folic acid supplementation had no effect in the decrease in hemoglobin or the measured parameters of hemolysis. No difference between males and females was noted for hemoglobin decrease or lowest hemoglobin levels. In our study, folic acid showed no beneficial effect in the prevention of ribavirin- induced anemia.

Key words: Hepatitis-C, Ribavirin, Anemia

Hepatitis C represents a significant cause of chronic liver disease. It is estimated that 170 million persons are infected worldwide. Its prevalence in the United States is approximately 1.8 % of the general population (1,2).

Interferon was the first medication approved for the treatment of chronic hepatitis C, however, only close to 16 % of those treated developed a sustained response (3). Ribavirin is a guanosine analogue that has been evaluated extensively as a therapy for Respiratory Syncytial virus and HIV infection in humans. Ribavirin in combination with interferon has an additive or synergistic effect on RNA viral replication, improving sustained response rates to about 40 % in treatment-naïve patients (4-6)

Dose-dependent hemolytic anemia is the most important adverse effect of ribavirin. Anemia most frequently occurs during the first 4 weeks of treatment but can occur at any time through out treatment. The usual hemoglobin decline is 2 to 4 g/dl within the first 4 weeks of therapy (7). Strategies to prevent hemolysis have not been published to our knowledge. In sickle cell anemia, folic acid supplementation is widely used with the purpose of improving erythropoiesis and decreasing hemolysis . Low erythrocyte folate levels have been reported and folate therapy has been found to increase hematocrit in some of these patients(8). Another study has suggested that there is no benefit from this therapy(9), and its routine use has been challenged (10,11).

The purpose of our study was to evaluate the effectiveness of FA supplementation in preventing ribavirin-induced hemolytic anemia in patients with hepatitis C receiving treatment with interferon and ribavirin.

Methods

Eighty patients enrolled in treatment protocols with interferon alfa-2b induction therapy and ribavirin at the University of Puerto Rico Hepatitis C Research Clinics from March 1998 to July 1998 were studied. Patients were assigned randomly to one of two treatment groups. One group received induction therapy with interferon alfa-2b 5 million units daily for 14 days followed by combination therapy with interferon alfa-2b 3 million units three times a week plus ribavirin to complete 48 weeks. The other group received combination therapy with interferon alfa-2b 3 million units three times a week plus ribavirin for 48 weeks. Ribavirin dose was 1,000 mg for patients weighting less than 70kg and 1,200mg for patients weighting $\geq$ 70kg. Recruitment for the folic acid supplementation study was made from the patients participating in the hepatitis C treatment protocol. After obtaining informed consent, subjects were randomized to receive either FA 1 mg daily

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or no supplementation (controls). Hemoglobin (Hgb), reticulocyte count, lactic dehydrogenase (LDH) and bilirubin levels were measured before starting therapy and at 2, 4, 6, 8,12, 16, 20 and 24 weeks of treatment. Ribavirin was reduced to 600 mg if Hgb decreased below 10 g/dL and discontinued if Hgb was below 8g/dL. In 24 patients, baseline and 24 week levels of haptoglobin and serum folate levels were available.

The protocol was approved by the Institutional Review Board of the University of Puerto Rico Medical Sciences Campus.

Statistical analysis. Continuous variables that were normally distributed were expressed as mean ± standard deviations (SD). Those variables without normal distribution were presented as mean and range. To determine differences between patients who received FA and those who did not, Student T- Test or Wilcoxon Two Sample Test, when appropriate, was used. To determine differences between categorical variables, Pearson Chi Square test was used. All statistical tests were two-sided. Epi-info version 6.04C (CDC, Atlanta, GA) was used for data entry and statistical analyses were performed using SAS software.

Results

Of the eighty patients randomized into the study, forty three completed it. Twenty one patients received FA and 22 did not. The two groups were similar in age, gender and dose of ribavirin. The mean age was 49 ± 7 years in the treatment group and 46 ± 8 years in the control group (p>0.05). There were 15 males and 6 females in the treatment group and 11 males and 11 females in the control group. Six patients received 1000 mg and 15 patients received 1200 mg of ribavirin in the treatment group; in the controls, 12 and 10 patients received respective doses of ribavirin. Comparison of the two groups in shown in Table 1.

Table 1. Study groups

	FA	C	p
	(n = 21)	(n = 22)	
Age (years)	49 ± 7	46 ± 8	p > 0.05
Gender (M/F)	15/6	11/11	p > 0.05
Ribavirin dose (1gm / 1.2gm)	6/15	12/10	p > 0.05

Changes in hemoglobin. Changes in hemoglobin after treatment are shown in Graph 1. Comparison of hemoglobin drop and nadir between males and females is shown in Table 2. No difference was demonstrated between males and females in the decrease in hemoglobin levels or the lowest hemoglobin value detected.

Figure 1. Changes in hemoglobin

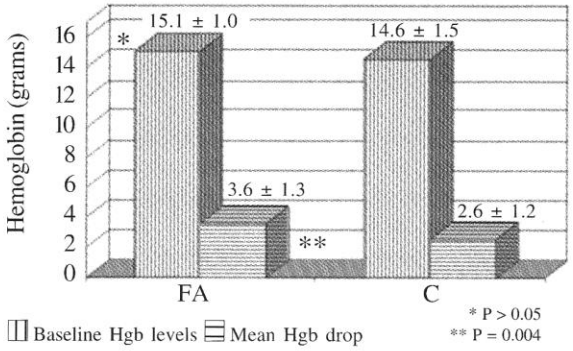

Table 2. Changes in hemoglobin

	FA	C	p
	(n = 21)	(n = 22)	
Mean Hgb drop	3.6+1.3	2.6+1.2	0.004
Male (g/dl)	3.9+1.3	3.1+1.5	>0.05
Female	3.05+1.3	2.3+0.9	>0.05
Mean Hgb nadir	11.5+1.3	11.9+1.5	>0.05
Male (g/dl)	11.7+1.2	12.7+1.7	>0.05
Female	10.9+1.3	11.5+0.7	>0.05

Hemolysis parameters. There was no difference in the parameters of hemolysis measured between patients receiving folic acid and controls, as shown in Table 3. Five patients required ribavirin dose reduction: 4 females and 1 male, all in the treatment group. Four patients had a decrease in reticulocytes and 12 patients (FA treatment group) had an increase in haptoglobin during ribavirin treatment.

Table 3. Hemolysis parameters

	FA	C	p
↑ Retic. count	4.4 %	4.4 %	>0.05
↑ LDH (mg/dl)	71±89	63±113	>0.05
↑ Bilirubin (g/dl)	0.5±0.3	0.5±0.8	>0.05
↓ Haptoglobin (mg/dl)	43±15	21±23	>0.05

Discussion

Ribavirin-induced hemolytic anemia is one of the most serious complications of the combination therapy with interferon plus ribavirin for hepatitis C (7). Our goal was to

determine if treatment with 1 mg of folic acid could reduce the degree of anemia induced by ribavirin. Our study failed to demonstrate any benefit from therapy. Contrary to the group treated with folic acid, there was a greater decline in hemoglobin levels as compared with the control group. One possible explanation for this finding is that ribavirin-induced anemia has been reported to be dose related (12). When we compared the randomization in both groups (treatment and control), there were more patients receiving 1,200 mg of ribavirin in the folic acid supplementation group (15 patients) as compared with the controls (10 patients), even though the total cumulative dose of ribavirin was the same in both groups. Since decline in hemoglobin correlates with the ribavirin dose, a larger number of patients receiving the higher ribavirin dose may account for the larger decline in hemoglobin in the FA-treated group as opposed to the controls.

Other factors may explain the lack of benefit from folic acid supplementation. The prescribed dose (1 mg) may be insufficient to improve erythropoiesis. Another explanation may be that folic acid supplementation is effective in promoting erythropoiesis only in folic acid deficient patients (8). All patients in the folic acid group had adequate serum folate levels. Erythocyte folate levels were not measured in our study.

Studies in Rhesus monkeys have shown that another mechanism for ribavirin-induced anemia is myelosuppresion. This mechanism may explain why in some of our patients, reticulocyte counts dropped instead of increasing and haptoglobin levels did not decrease at all (12,13).

McHutchison demonstrated that the opportunities of achieving a sustained virological response are better with strong adherence to both interferon and ribavirin during therapy. For this reason, a prompt and effective control of side effects to avoid dose reduction or discontinuation of treatment is important(14).

The hematopoietic growth factor erythropoietin has demonstrated its usefulness improving hemoglobin levels and allowing a greater total ribavirin dose to be received by patients with fewer dose reductions during treatment (15), and his now used frequently. However, erythropoietin is very expensive and not readily available for all patients.

One of the leading hypotheses about the mechanism of ribavirin-induced anemia is the accumulation of ribavirin in the red cell, leading to membrane oxidative damage (16). Brass suggested that the concurrent use of over-the-counter antioxidants (vitamin C and vitamin E) during treatment with interferon alfa-2b/ribavirin could delay the ribavirin-induced anemia at least during the first several weeks of combination treatment. The effect was lost after the 12th week of therapy (17).

Our study failed to demonstrate any benefit from folic acid 1 mg daily in preventing or ameliorating ribavirin-induced anemia. Further efforts must be made to find a more affordable way to reduce this serious side effect of ribavirin because of the possible cardiac and cerebrovascular complications of severe anemia and the decreased effectiveness of combination therapy in hepatitis C when dose modification has to be made.

Resumen

El tratamiento de hepatitis C consiste de interferón alfa en combinación con ribavirina. El efecto adverso principal de ribavirina es la anemia hemolítica, una complicación que limita la terapia. La suplementación con ácido fólico se utiliza para mejorar la eritropoiesis en anemia hemolítica crónica. El propósito de este estudio fue determinar la efectividad de suplementación con ácido fólico en la prevención de anemia inducida por ribavirina en pacientes bajo tratamiento para hepatitis C. Veintiún pacientes en protocolos de tratamiento para hepatitis C recibieron ácido fólico (1 mg diario) y veintidós no lo recibieron. Los grupos eran similares en edad, sexo, dosis de ribavirina y hemoglobina inicial. La suplementación con ácido fólico no tuvo ningún efecto sobre la disminución en hemoglobina o los parámetros de hemólisis medidos. No hubo diferencia entre varones y hembras en la disminución de hemoglobina ni el valor más bajo detectado. En este estudio, el ácido fólico no demostró beneficio en la prevención de anemia inducida por ribavirina.

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