

Camel Milk with Pegylated Interferon Alfa-2a and Ribavirin for Treatment-Naive Chronic Hepatitis C Genotype 2/3: An Open-Label, Randomized Controlled Trial

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Abstract

Background: Chronic hepatitis C is one of the most important causes of cirrhosis and hepatocellular carcinoma (HCC). Camel milk (CM) is a new candidate therapy for chronic hepatitis C (CHC).

Objectives: The present study assessed the safety and efficacy of pegylated interferon alfa-2a and ribavirin with CM (CM + Peg IFN/RBV) and without CM (Peg IFN/RBV) in CHC genotype 2/3 infections.

Methods: This study was an open-label, randomized, phase 2 trial. Sampling strategy and date was computer-generated randomization. The researchers randomly selected 45 adult patients (ages > 18 years), who were treatment-naive with CHC infection (non-cirrhotic) to receive Peg IFN/RBV with standard-dose alone (group A, n = 23), CM + Peg IFN/RBV: 500 cc orally per day (group B, n = 22) for 24 weeks in Iran. The primary efficacy outcomes were early virological response (EVR₁₂) and end-of-treatment response (ETR₂₄), the secondary efficacy outcome was sustained virological response (SVR₂₄), and the safety outcomes were adverse events and laboratory tests at end-treatment to assess.

Results: The EVR₁₂ was 60% (12/20), ETR₂₄ 90% (18/20), and SVR₂₄ 100% (18/18) of CM + Peg IFN/RBV therapy. The EVR₁₂ was 15% (3/20), ETR₂₄ 70% (14/20), and SVR₂₄ rates were 71% (10/14) in Peg IFN/RBV therapy (P < 0.05). Rates of discontinuation due to adverse events were 8.6% (2/23) in control and no discontinuation in intervention group. The most common adverse events were fatigue, anemia, and insomnia.

Conclusions: Combination of CM with Peg IFN/RBV for 48 weeks showed significant improvements in the viral response and decreased adverse effects in CHC genotype 2/3 (P < 0.05). The data of the study supported the CM synergistic antiviral activity of Peg IFN/RBV. Large clinical trials are needed to confirm the results.

Keywords: Camel Milk, Iran, HCV Genotype 2/3, Chronic Hepatitis C

1. Background

Chronic Hepatitis C is one of the most important causes of cirrhosis and hepatocellular carcinoma. It has been evaluated that there are more than 200 million patients chronically infected with hepatitis C virus (HCV). The prevalence HCV in Iran is estimated to be less than 1.5%. Standard treatments are peginterferon alfa-2a and ribavirin. Protease inhibitors (telaprevir or boceprevir) were the first oral anti-HCV drugs in combination with peginterferon and ribavirin, yet new anti-HCV drugs include: sofosbuvir, daclatasvir, and ledipasvir without peginterferon, which are very expensive (1-4). However, some patients do

not respond to these treatments. Besides, the side effects of these drugs and ban on their use in some patients have made the treatment of hepatitis C difficult. Therefore, the introduction of new, safe, and effective drugs with no side effect for this disease could be considered (5, 6).

Traditional experiences of Asian, African, and Indian countries confirm many therapeutic effects of camel milk on various diseases, including liver diseases. Also, the main focus of most of the modern medicine researches conducted on camel milk effects is on the liver. Recent findings have shown antiviral effects of natural materials, such as CM against the hepatitis C virus (7). Special bioactives along with camel immune system and its transfer

to milk causes the milk to have pharmacological effects in favor of the liver, including protective effects against viral and bacterial agents, chemical, and toxic substances. Camel milk has potent immunological, anti-allergic (5), antioxidant agent (8), antibacterial (9), anti-diabetic (9), and anti-inflammatory (10), immunomodulatory (5), anti-apoptosis (11), and anticancer properties (12). It contains various mineral, vitamins, protective proteins, and essential fatty acids, indicating the potential therapeutic effects underlying the anti-HCV actions. Camel's immune system is different from most mammals and is much stronger than the human's immune system. For example, camel milk has a particular class of antibodies and immunoglobulins, which are only composed of heavy chains and lack light chains in their structures. These immunoglobulins (simple structure, high affinity, and specificity of these compounds, as antiviral agents) help in the reinforcement of patient's immune system. Therefore, CM could be a new candidate for complete treatment of HCV infections.

2. Objectives

The present study assessed the safety and efficacy of CM in combination with pegylated interferon alfa-2a and ribavirin in CHC genotype 2/3 infections in Iran.

3. Methods

3.1. Study Design and Participants

For this open-label clinical trial, inclusion criteria were age of between 18 and 60 and presence of chronic infection with genotype 2/3 HCV, with plasma HCV RNA positivity. Patients were treatment-naive in Iran (Mashhad) and non-cirrhotic, as determined by the following: Fibro scan > 12.5 kpa, or Fibro Test > 0.75. Patients with the following criteria were excluded: BMI < 18 kg/m², autoimmune disease, evidence of cancer, human immunodeficiency virus (HIV) or HBV infection, neutropenia (neutrophils less than cells/mm³ 1500), thrombocytopenia (platelets < cells/mm³ 90000), creatinine levels greater than 1.5 times the normal level, clinically significant bleeding disorders, organ transplant, severe heart disease, chronic pulmonary disorder, uncontrolled psychiatric illness, epilepsy, retinopathy, active alcohol or drug abuse, pregnancy and lactation, anemia (hemoglobin less than 10), systemic bacterial or fungal infection, failure to comply with the prescribed dose of milk, discontinued participation in the study and other genotypes of HCV.

The study was based on the ethical principles of Helsinki, and was approved by the ethics committee of Mashhad University of Medical Sciences, Iran (No: 922662).

All participants completed and signed an informed consent form before the start of the study. Trial registration: ClinicalTrial.gov, NCT02216045.

3.2. Randomization and Masking

The researchers used a computer-generated randomization sequence. Patients were randomly allocated with a 1:1 ratio to 2 groups (with a block size of 4) by a centralized computer algorithm. This was an open-label clinical trial, so patients and investigators were not masked for treatment allocation.

3.3. Procedures

Among the trial patients with chronic HCV infection, there were 2 groups: Group A was the control group and received Peg IFN/RBV, and Group B was the intervention group and received CM + Peg IFN/RBV for 24 weeks. Oral consumption of CM 2 times, at 8:00 am and 20:00 am with 250 cc per serving was prescribed. Furthermore, Peg IFN and RBV with a standard dose were given. Subcutaneous injections of 180-mg of pegylated IFNa-2a (Pegasys; F. Hoffman-LaRoche) and daily weight-based oral ribavirin (Copegus; F. Hoffman-LaRoche) were also administered. Camel milk was collected from the Livestock company of Iran, and packaged in sterile bottles and then transported in cool boxes to the research center.

The primary efficacy outcomes were early virologic response (EVR12: HCV RNA ≥ 2 log₁₀ on week 12) and end-of-treatment virologic response (ETR24: undetectable HCV RNA on week 24). Secondary efficacy outcomes were sustained virological response (SVR24: HCV RNA undetectable during week 48). Plasma HCV RNA was analyzed using quantitative Real Time-Polymerase Chain Reaction (RT-PCR) the Roche COBAS TaqMan HCV Test (v2.0). Results are expressed in copies/mL and indicate the activity of HCV and virus replication in the patient.

Safety data was collected at the beginning and end of treatment. Criteria for the side effects used "common terminology criteria for adverse events v4.0 (CTCAE)". The data adverse events included history and physical examination, clinical laboratory tests and electrocardiogram.

3.4. Statistical Analysis

The sample size was estimated as 45 considering probable patient loss (α type error of 0.05 and β error of 0.20 on the assumption of 65% SVR₂₄ in group A and of 90% SVR₂₄ in group B) and formula

$$n = \frac{p_1(100 - p_1) + p_2(100 - p_2)}{(p_2 - p_1)^2} \int (\alpha, \beta) \quad (1)$$

Data were analyzed by the SPSS software (version 16). Data were expressed as mean \pm standard deviation (SD).

Some variables did not have a normal distribution thus the nonparametric method was used. Friedman, Mann-Whitney, and Wilcoxon test were used for analysis. $P < 0.05$ was considered as statistically significant.

4. Results

From June, 2014 to February, 2015, 75 patients were referred to 2 liver treatment centers (governmental) in Iran, and after screening, 45 patients were enrolled in the study. Thirty patients did not meet the study inclusion criteria for reasons of out of range age (no = 5), cirrhosis (no = 10), severe heart disease (no = 5), active drug abuse (no = 5), hyperthyroidism (no = 4), declined to participation (no = 2), and no 2@3 genotype virus (no = 2). All patients except 5 completed the treatment for reasons of loss to follow-up (no = 3) and adverse events (no = 2) (Figure 1). Baseline characteristics of patients in the 2 groups was similar and there was no difference in distribution (Table 1). The EVR₁₂ of the intervention group was 60% and for the control group, this was 15%. The EVR₂₄ in intervention group was 90%, and in the control group, this was 70%. The response of the intervention group was 20% higher than the control group. The analysis of results showed a significant reduction in viral load in each group ($P < 0.05$). The SVR₂₄ in the intervention group was 100% (18/18) and in the control group, this was 71% (10/14). Comparison of the 2 groups showed the difference was significant ($P < 0.05$) (Table 2).

4.1. Safety and Tolerability

No patients discontinued treatment due to adverse events in the intervention group, yet 2 patients in the control group (8.7%; 2 out of 23) discontinued treatment due to a serious adverse event, including severe depression (1 patient) and hyperthyroidism (1 patient). In both groups some patients experienced a degree of loss of appetite, insomnia, fatigue and depression, yet at the end of treatment, these complaints changed in both groups. At the end of treatment, in the intervention group complaints of appetite, insomnia, and fatigue had improved, yet they had increased in the control group. Some decrease in white blood cells, platelets, and hemoglobin were observed in both groups (Table 3).

5. Discussion

The results presented here indicate that 24 weeks of 250 cc of CM twice a day with Peg IFN/RBV achieved EVR₁₂, ETR₂₄, and SVR₂₄ of 60%, 90%, and 100%. Peg IFN/RBV achieved EVR₁₂, ETR₂₄, and SVR₂₄ of 15%, 70%, and 71%. Higher levels of ETR₂₄ and SVR₂₄ could be attributed to differences

Table 1. Demographic, Biochemical, Serological, and Molecular Profile of Patients with Chronic Hepatitis C at Baseline

Characteristics	CM + PegIFN/RBV	PegIFN/RBV	P Value
Demography No. (M/F)	20 (14/6)	20 (14/6)	$P > 0.05^b$
Body weight (kg)^a	78.65 (± 4.68)	78 (± 6.49)	$P > 0.05^c$
Mean age (yr.)^a	47.50 (± 10.62)	49.50 (± 10.14)	$P > 0.05^c$
Risk factor for transmission			$P > 0.05^c$
Transfusion-related	0	1 (5)	
Intravenous drug abuse, No. (%)	10 (50)	10 (50)	
Other (sexual, tattoo, occupational), No. (%)	3 (15)	1 (5)	
Unknown, No. (%)	7 (35)	8 (40)	
Biochemistry^{a,d}			
ALT, U/L	106.35 (± 40.97)	122.25 (± 40.99)	$P > 0.05^c$
AST, U/L	92.35 (± 27.09)	113.55 (± 30.59)	$P > 0.05^c$
Serology			-
HBSAg	0	0	
Anti-HCV	58.5	59	-
Anti-HIV-1 and -2	0	0	-
Molecular			$P > 0.05^c$
HCV genotype (2; 3)	3; 17	5; 15	
Pretreatment HCV			$P > 0.05^b$
RNA ^{a,e} , 10 ⁶ copies/mL	2.60 (± 3.42)	2.43 (± 4.10)	

^aValues are expressed as mean (± SD).

^bFisher's exact test.

^cChi-Square test.

^dNormal reference ranges: 4 to 23 U/L for ALT, 6 to 18 U/L for AST, 3.4 to 20.5 mmol/L.

^eRNA: 10⁶ copies/mL.

in immunity status between various populations. All of the patients were white Iranians, therefore, race had no impact on the results of the current study.

Patients with viral load of $< 2 \times 10^6$ Copy/mL showed better therapeutic responses, yet in the current study no significant correlation was found between viral load and therapeutic response due to the normal distribution of the 2 groups, and mean viral loads were higher than 2600771.25 in the case and 2438350 in the control group (higher than 2×10^6 Copy/mL).

Consumption of alcohol is associated with lower ther-

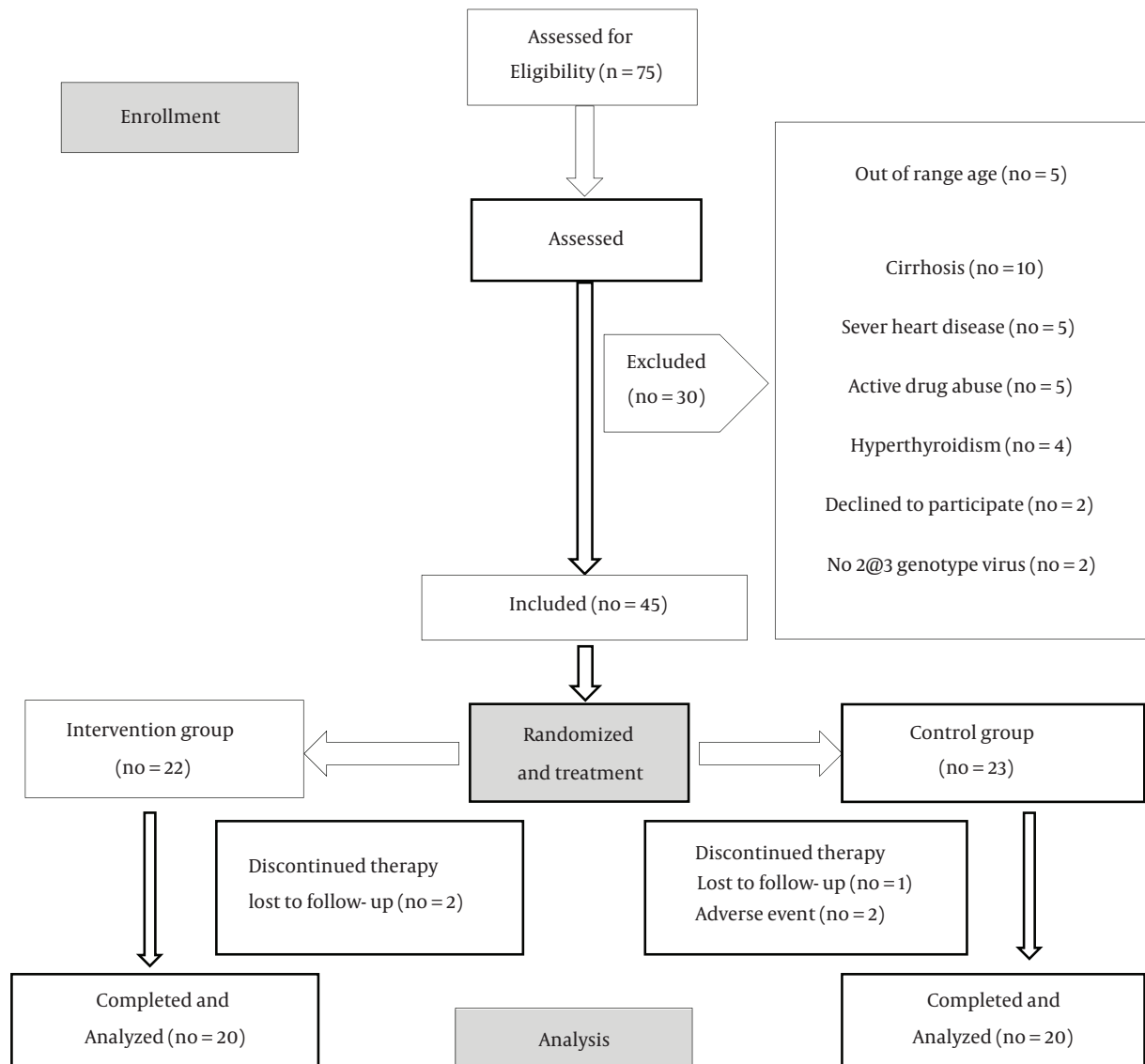


Figure 1. Flow Chart Study

apeutic response. In the current sample, alcohol intake was not common and alcohol intake in both groups was excluded. It seems that the mean age of the patients (< 50 years) in the current study was another reason for higher therapeutic response. However, due to the normal distribution, age had no significant effect on the results.

Receiving a proper dose of ribavirin is effective in treatment response. In the current study, 25% of the patients in both groups were over 75 kg and received a full dosage. With observing the appropriate dosage and normal distribution of the patients in both groups, weight had no confounding effect on the outcome.

Another probable reason for stronger response to the treatment could be attributed to the use of CM. Camel immunoglobulins are secreted in the blood and then into milk, and it is known as a substance that empowers the immune system (13).

Several studies reported the protective and therapeutic effects of camel milk on the liver of mice exposed to carbon tetrachloride (14), alcohol (15), and gentamicin (16). In all cases, normalization of liver enzymes and recovery of live tissue has been accessed. Therefore, decreased aspartate aminotransferase (AST) and Alanine Transferase (ALT) is associated with the ability of camel milk to protect the struc-

Table 2. Virologic and Biochemical Responses during Treatment and End of Treatment (Week 12, 24, and 48)^a

Time of Study	CM + Peg IFN/RBV No. (%)	Peg IFN/RBV, No. (%)	P Value ^a
Virologic Response			
Wk. 12 (CEVR ₁₂)	12 (60)	3 (15)	P > 0.05
Wk. 24 (ETR ₂₄)	18 (90)	14 (70)	P > 0.05
Wk. 48 (SVR ₂₄)	18/18 (100)	10/14 (71)	P < 0.05
Biochemical Response (ALT)			
Wk. 12	13 (65)	15 (75)	P > 0.05
Wk. 24	19 (95)	17 (85)	P > 0.05
Biochemical Response (AST)			
Wk. 12	16 (80)	5 (30)	P < 0.05
Wk. 24	19 (95)	14 (70)	P > 0.05

^aChi-Square test (compare the two groups).

tural integrity of the hepatocytes and to recover the damaged hepatocytes.

Redwan et al. (2014) showed that camel milk's lactoferrin might be one of the main components of CM that has anti-viral properties. They also stated that camel milk's lactoferrin is much more efficient than lactoferrin from human and cow's milk, which prevents the HCV to enter leukocytes and human HepG2 cells (17, 18). El-Fakharany from Egypt (2012) showed that camel milk polyclonal antibody has destructive viral peptides and growth inhibitory effects yet human immunoglobulin and casein have not been affected (19).

Yalin Liao et al. (2012) showed the inhibitory effect of native and recombinant lactoferrin of camel milk on HCV infection on the Huh7.5 cells. This study suggests that lactoferrin prevents the entry of virus in the cell through direct interaction with HCV and inhibition of virus amplification (20). The current results are also consistent with the findings of a study by Seher Abbas et al. (2014) that explored the potential of camel milk on blood parameters and liver function of patients with hepatitis. Similar to the current study, ALT, AST, and ALP levels were reduced and inhibited the reduction of platelets, white blood cells, and hemoglobin (21).

In a human study on hepatitis B, it was shown that taking CM improves cellular immunity and interferon level, and inhibits viral proliferation, resulting in greater improvement in chronic hepatitis B patients (22). In another human study on 25 patients with HCV in Egypt, it was shown that drinking CM for 60 days as an adjunctive therapy to the standard treatment of PEG/RBV significantly elevated the serum levels of albumin, anti-apoptotic protein

BCL-2, total antioxidant capacity, interleukin-10, and vitamin D ($P < 0.001$) (23).

Furthermore, CM, as a supplement food, containing the substances required for the body, is an effective element in therapeutic response improvement. Results of a study conducted on 31 patients to investigate the role of vitamin D, suggested that the intake of 2000 units of vitamin per day, significantly decreased AST enzyme and viral load. According to this study, deficiency of vitamin D affects the response to treatment; therefore, vitamin D supplementation could contribute to better responses (24). Vitamin content of camel milk could play a role in response improvement. Results reported that camel milk contained higher levels of B2, C, D, and niacin (5).

The current study is consistent with Al-Hashem et al.'s (2009) report that addressed the role of camel milk in rates of exposure to aluminum chloride, a substance that destroys red blood cells and hemoglobin and leads to hematocrit reduction. In this study, daily consumption of CM for 30 days effectively increased the number of red blood cells and corrected hemoglobin and hematocrit level (25).

The strength of this study was the use of natural acceptable food with conventional treatment and the limitation of this study was the low number of patients. Results suggested that the therapeutic response of pegylated interferon alfa-2a and ribavirin was acceptable, however, camel milk could be used to increase therapeutic response and decrease complications. Camel milk is recommended as a safe complementary therapy that could be added to standard antiviral drugs to increase their safety and effectiveness in CHC.

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Footnotes

Authors' Contribution: All authors contributed equally to this project and article. All authors read and approved the final manuscript.

Consent for Publication: All participants completed and signed an informed consent form before the start of the study.

Trial Registration: This study was registered as follows; clinicalTrials.gov, NCT02216045.

Availability of Data and Material: All data of the test and control patients are available from the authors.

Table 3. Rates of Discontinuation of Treatment, Dose Reductions, and Adverse Events during Treatment^a

Adverse Event	CM + PegIFN/RBV First of Treatment	CM + PegIFN/RBV End of Treatment	P Value ^b	PegIFN/RBV First of Treatment	PegIFN/RBV End of Treatment	P Value ^b
Discontinuation of treatment for adverse event	-	0	-	-	2	-
Dose reductions	-	0	-	-	0	-
Adverse Events						
Fatigue	7/20 (35)	6/13 (30)	0.010	6/20 (30)	10/20 (50)	P > 0.05
Insomnia	4/20 (20)	3/20 (15)	0.564	2/20 (10)	7/20 (35)	P < 0.05
Depression	4/20 (20)	5/20 (25)	0.705	4/20 (20)	7/20 (35)	P < 0.05
Loss of appetite	11/20 (55)	4/20 (20)	0.705	10/20 (50)	12/20 (60)	P < 0.05
Laboratory Abnormalities						
Hemoglobin, < 12 g/dL	0/20	2/20 (10.0)	0.157	0/20	8/20 (40)	P < 0.05
Platelet, < 120000 cells / mm ³	0/20	3/20 (15.0)	0.830	0/20	7/20 (35)	P < 0.05
White blood cell, < 4000 cells / mm ³	0/20	6/20 (30.0)	0.014	0/20	8/20 (40)	P < 0.05

^aValues are expressed as No. (%).

^bWilcoxon test (compare the intergroup).

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