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Original article

Effect of chloroquine on some clinical and biochemical parameters in non-response chronic hepatitis C virus infection patients: pilot clinical trial

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Summary. *Background:* Hepatitis C virus infection frequently leads to chronic hepatitis C which may progress to cirrhosis and can be ended to hepatocellular carcinoma. This study aimed to investigate the effect of Anthropometric Parameters, Vit D3, Thyroid Function, Ferritin and Biochemistry Parameters in patients chronically infected with HCV with non-response criteria which was treated by chloroquine. *Methods:* This study was the continuation of our previous investigation with a triple-blind method in a randomized controlled pilot study. After understanding the study procedures, patients signed an informed consent form and were randomized into the treatment (chloroquine 150 mg once daily, for 8 weeks) and control (placebo once daily, for 8 weeks) groups. The inclusion criteria were male, between 18 and 60 years of age, confirmed chronic hepatitis C with non-response criteria, and Genotype 1. Data were analyzed with an intention to treat perspective at the end follow up (12 weeks) considering to variables such as anthropometric parameters, Vit D3, thyroid function, ferritin and biochemistry parameters evaluated. *Results:* Although decreases in total weight (P-value=0.4), mid-arm circumference (P-value=0.05), and body mass index (P-value=0.04), increases in total body fat (P-value=0.8) and triceps skin fold thickness (P-value=0.7) in the intervention group compared to the control group were observed. Moreover, a reduction of AST (P-value=0.30), ALT (P-value=0.10), cholesterol (P-value=0.005), triglyceride (P-value=0.40) and ferritin (P-value=0.030) levels was observed in the intervention group during the follow up period. Our results also showed that serum TSH levels (P-value=0.5) were slightly higher in the chloroquine group than in the placebo group, though the trend was reversed for T3 (P-value=0.05) and T4 (P-value=0.04) levels. However, median of T3 and T4 were similar in both groups. A significant increase in vitamin D levels from 15 to 34 ng/ml was observed in the chloroquine group (P-value=0.04). *Conclusion*s: The results suggest that chloroquine therapy may be very useful for HCV treatment in patients with non-response criteria, and helps to normalize some anthropometric parameters, biochemical, ferritin, and vitamin D status. (www.actabiomedica.it)

Key words: anthropometric parameters, thyroid function, biochemical parameter, chronic hepatitis C virus, non-response patients, chloroquine, vitamin D, ferritin

Introduction

Hepatitis C virus (HCV) infection is a worldwide public health problem(1). HCV infection frequently leads to chronic hepatitis C (CHC), which may progress to cirrhosis and even to hepatocellular carcinoma (HCC) (1). Currently, aside from the established consequence of liver injury, chronic hepatitis C virus (HCV) infection is associated with some adverse changes in metabolic and biochemical parameters such as lipid and liver profile values (2-4). Some studies have highlighted the association between HCV infection anthropometric parameters (2-3, 5-6). Other studies have highlighted the relationship between biochemistry parameters (4, 7) or thyroids functions (8) along with the HCV virus infection. It is notable that HCV infected patients have impaired liver function which will affect ferritin storage (9). Serum ferritin is the inflammation marker in impaired liver function and is a marker to show the status of liver inflammation. The elevated serum ferritin may cause liver fibrosis (9). In addition, the relation between vitamin D level and chronic liver diseases has also been described (10). Recently, an association between vitamin D status at the time of starting therapy in HCV infected patients and achievement of sustained virological response (SVR) following treatment of chronic or recurrent HCV was described (11). It was reported that patients with severe vitamin D deficiency almost never achieved SVR, while those with near-normal or normal vitamin D level gained an SVR rate in about half the cases (12). Recent studies have found that vitamin D supplement enhanced the probability of achieving an SVR following antiviral therapy, providing direct evidence for the causal relationship between vitamin D and HCV infection (13-15). Thyroid function involvement has been reported in HCV patients (16). Abnormality in thyroid activity has been related with liver damage, and a recent study demonstrated a direct relationship between thyroid-stimulating hormone serum levels and ALT levels even within a normal range of TSH values. In addition, some evidences documented the presence of active TSH in the human liver (17-19).

Therefore, all of the above mentioned parameters have important roles in HCV patient therapy and progress in their liver disease. Few studies have evaluated anthropometric parameters, Vit D3, thyroid function, ferritin and biochemistry parameters in non-response patients (20) with chronic hepatitis C virus infection together, and in addition, there are no studies which assess all the mentioned parameters in association with chloroquine (CQ) therapy for HCV patients with non-response criteria. Therefore, the present study aimed to investigate the associations between parameters in patients chronically infected with HCV with non-response criteria which were treated by chloroquine.

Patients and Methods

Patients

Current investigation is the continuation of our previous paper *"New use of an old drug: cloroquine reduces viral and ALT levels in HCV non-responders"* (20). We prospectively enrolled 10 non-response patients with chronic HCV from the Hepatology Clinic of Shiraz University of Medical Sciences (ClinicalTrials.gov Identifier: NCT02058173). The enrolled patients were male, between 18 and 60 years of age, affected by confirmed chronic hepatitis C with non-response criteria, genotype 1, and understood the study procedures, signing informed consent forms.

Study design

This was a triple-blind, randomized controlled pilot study. Patients were randomized into the treatment group, which received 150 mg of chloroquine once daily for 8 weeks, and the control group, which received a placebo once daily for 8 weeks. Further details of the study design are available in our previous paper (20). Anthropometric parameters, vitamin D3, thyroid function, ferritin and biochemistry parameters were compared and evaluated between the groups at the commencement of the study, as well as during the first, second and final (third/post-treatment) follow-ups which occurred at 4, 8 and 12 weeks respectively.

Parameters assessments

Anthropometric evaluation

Body composition was measured through electric impedance technique (InBody 3.0, Biospace, Inc). Before evaluations, patients were asked to fast at least 8 h, avoid any type of exercise for 5 days, and empty their bladder and bowels (21,22). The parameters evaluated in body composition were body mass index (BMI) (kg/m2), total body fat (TBF), waist circumference (WC), Mid-arm Circumference (MAC) and Triceps Skin Fold thickness (TSF) (2). All measurements were performed by the same researcher. All subjects had their weight (kg), height (m) and waist and hip circumference (cm) measured. Measurements were taken by the same trained interviewer at the end of the interview, following a uniform protocol that included repeated measurements on each subject. Weight was to the nearest 0.1 kg on a balance scale (Model #Seca Scale). Standing height was measured to the nearest 0.1 cm with a wall-mounted stadiometer. Body mass index (BMI), as classified by international centers, was used to assess adiposity. Waist circumference (WC) was measured, using a flexible plastic tape, 2 cm above the umbilicus with the subject standing. Hip circumference was measured at the maximum width in the hip area over light clothing. WHR index was assigned to assess central fat distribution.

Biochemical profile

Blood samples were obtained from all patients after overnight fasting. Samples were centrifuged and sera were stored at -25°C. The biochemical profile included AST (aspartate aminotransferase) and Alanine Aminotransferase (ALT), with the lipid profile including cholesterol and triglycerides (TG). Routine biochemical tests were performed using manual enzymatic assays. All biochemical tests were done in the same laboratory following standard laboratory methods.

Thyroid function assessments

Thyroid function tests, including serum thyrotropin (TSH), total thyroxine (TT4) and total triiodothyronine (TT3) were assessed through an Enzyme Immunoassay (EIA, Ideal Tashkhis, Iran).

Others (serological levels of 25-OH vitamin D and ferritin assessments)

Serums of all patients were collected and frozen for analyzing 25-OH vitamin D by EUROIMMUN 25-OH Vitamin D ELISA kit (Luebeck, Germany) and ferritin evaluation was performed through an Enzyme Immunoassay (EIA, Ideal Tashkhis, Iran).

Statistical analysis

Variables were described by mean ± SD, minimum and maximum values as indicated. Data were analyzed in order to treat perspective, i.e. including all patients who received at least one dose of the study drug. Data collection was fairly complete. In accordance with the non-normal distribution of data and the small sample size of this study, the Mann-Whitney U test was used to detect the significant difference between control (placebo) and treatment (intervention) groups. The Friedman test was used to detect the trends of parameters during the follow-up period within the groups, and the Wilcoxon signed-rank test was used to compare the differences between parameters in two time periods during the follow-up. All statistical analysis was performed using SPSS for Windows (Version 10 SPSS Inc, Chicago, IL, USA). P-values less than 0.05 were considered as statistically significant.

Results

The characteristics and clinical data of patients

All patients were male and patients' baseline characteristics are illustrated according to age, anthropometric parameters (BMI, weight, TBF, WC, MAC, and TSF), biochemistry parameters (AST, ALT, Cholesterol, and TG), thyroid function, and others (ferritin and Vit D) in Table 1.

Anthropometric evaluation

The anthropometric data at baseline is presented in Table 2. Regarding anthropometric variables, weight, MAC, and BMI were decreased in cases after intervention compared to the control group.

Table 1. Demographic and clinical baseline characteristics of none-responders patients with hepatitis C virus

Characteristics	Groups		P.value*
	Control (Placebo) (n=4)	Treatment (Intervention) (n=6)	
Demographic			
Age (years)	50± 3	47± 11	0.70
Anthropometric parameters and body composition [a]			
BMI (kg/m^2)	23 (22-27)	24 (21-25)	0.60
Weight (kg)	64 (60-78)	70 (57-88)	1.0
TBF (%)	7 (6-11)	6 (5-7)	0.20
WC (cm)	86 (67-98)	87 (83-89)	1.0
MAC (cm)	29 (27-32)	31 (22-33)	0.50
TSF (cm)	8 (5-10)	6 (4-11)	0.70
[a] Biochemistry Parameters			
AST levels (U/l)	47 (39-48)	48 (26-76)	0.80
ALT levels (U/l)	44 (32-56)	57 (13-95)	0.70
Cholesterol (mg/dL)	154 (133-177)	144 (113-184)	0.80
TG (mg/dL)	98 (84-152)	86 (50-143)	0.30
[a] Thyroid Function			
T3 (ng/ml)	1.70 (1.40-2.0)	1.70 (1,60-2.20)	0.50
T4 (micg/dl)	9.70 (8.70-10.0)	11 (8.50-10.70)	1.0
TSH (mIU/ml)	1.1 (.10-1.90)	2.0 (.60-17.0)	0.10
[a] Others			
Ferritin (ng/ml)	188 (131248)	144 (30-210)	0.20
Vit D (ng/ml)	20 (17-35)	15 (8-27)	0.10

[a] Values are given as median (minimum-maximum)
*= Mann- Whitney U test

A decrease in total weight (70 to 63 kg) (P-value=0.4), MAC (31 to 25 cm) (P-value=0.05) and BMI (24 to 22 kg/m^2) (P-value=0.04) in the intervention group compared to the control group was observed. WC measurement decreased in the intervention group compared to the control group (Table 2).

Between the baseline and final follow-up measurements, the TBF of the intervention group increased from 6 to 8% and their TSF thickness increased from 6 to 7 cm (Table 2).

Biochemistry and ferritin

Measurements at the end of the first follow up (week 4) and second follow up (weeks 8-end of treatment) showed a decrease in median AST, ALT, Cholesterol, TG and ferritin levels in plasma samples of CQ-treated patients. Namely, a reduction of AST from 48 to 33 U/I (P-value=0.30), ALT from 57 to 42 U/I (P-value=0.10), cholesterol from 144 to 131 mg/dL (P-value=0.005), TG from 86 to 67 mg/dL (P-value=0.40) and ferritin from 122 to 106 ng/ml (P-value=0.030) was observed in the intervention group between the baseline and end of treatment (second follow-up) values (Table 2).

Persistent loss of parameters levels at final follow up (week 12) was observed only for ferritin levels in patients of the chloroquine group compared to the placebo group (Table 2 and Figure 1). However, for other biochemistry parameters, persistent loss at final follow up (week 12) was not observed.

Although persistent decrease of AST, ALT, Cholesterol, TG RNA level at the end of the 12 week follow up period was not observed in any of the patients in either group, the median AST, ALT, cholesterol, TG levels at the end of the follow up was lower (AST 36, ALT 46, cholesterol 142, TG 85) in the control group, compared to baseline (AST 48, ALT 57, cholesterol 144, TG 86) (P= 0.68, P= 0.03, P= 0.04, P= 0.30 respectively) (Table 2).

Table 2. Biochemistry and anthropometric parameters trend of change during chloroquine treatment

Parameters[a]	Control (Placebo) Group (n=4)						Treatment (Intervention) Group (n=6)					
	Baseline	first follow up	Second follow up	Third follow up	P-Value†	P-Value†	Baseline	first follow up	Second follow up	Third follow up	P-Value†	P-Value†
BMI (Kg/m2)	23 (22-27)	24 (22-26)	25 (22-27)	22 (22-26)	0.30	1.0	24 (21-25)	22 (20-24)	22 (20-24)	24 (21-24)	0.09	0.04
Weight (kg)	64 (60-78)	64 (60-78)	64 (61-79)	61 (61-77)	0.90	0.30	70 (57-88)	70 (54-81)	67 (55-76)	63 (56-76)	0.10	0.40
TBF (%)	7 (6-11)	8 (6-11)	8 (6-10)	6 (6-10)	0.80	0.50	6 (5-7)	7 (5-10)	7 (3-10)	8 (6-10)	0.40	0.80
WC (cm)	86 (67-98)	87 (69-100)	84 (65-98)	89 (83-96)	0.50	0.50	87 (83-89)	85 (80-93)	84 (79-90)	85 (78-86)	0.10	0.50
MAC (cm)	29 (27-32)	29 (25-100)	28 (25-31)	27 (26-31)	0.60	0.60	31 (22-33)	26 (22-33)	26 (21-31)	25 (21-31)	0.02	0.05
TSF (cm)	8 (5-10)	8 (4-11)	8 (6-9)	7 (7-9)	0.50	0.80	6 (4-11)	7 (3-12)	7 (4-13)	8 (5-10)	0.80	0.70
AST (U/I)	47 (39-48)	49 (41-2)	44 (39-66)	47 (39-62)	0.70	0.75	48 (26-76)	36 (28-43)	33 (28-45)	36 (27-68)	0.30	0.68
ALT (U/l)	44 (32-56)	59 (39-76)	60 (26-98)	56 (42-86)	0.30	0.60	57 (13-95)	50 (14-7)	42 (15-72)	46 (25-95)	0.10	0.03
Cholesterol (mg/dL)	154 (133-177)	148 (140-162)	148 (142-216)	163 (149-195)	0.80	0.20	144 (113-184)	134 (102-154)	131 (99-154)	142 (95-164)	0.005	0.04
TG (mg/dL)	98 (84-152)	136 (68-277)	226 (94-398)	198 (80-672)	0.30	0.10	86 (50-143)	80 (53-103)	67 (45-107)	87 (39-97)	0.40	0.30
Ferritin (ng/ml)	188 (131-248)	163 (110-236)	183 (129-290)	140 (100-321)	0.20	0.68	144 (30-210)	121 (28-191)	106 (33-159)	80 (26-187)	0.40	0.30
T3 (ng/ml)	1.70 (1.40-2.0)	1.60 (1.40-2.60)	1.20 (0.90-2.60)	1.80 (1.0-2.50)	0.05	1.0	1.70 (1,60-2.20)	1.50 (.30-1.80)	1.40 (0.90-1.90)	1.50 (1.40-1.70)	0.01	0.05
T4 (micg/dl)	9.70 (8.70-10.0)	10.20 (8.20-13.0)	11 (9.10-12.0)	8.90 (8.50-12.50)	0.90	0.20	11 (8.50-10.70)1	0.35 (8.40-12.0)	10 (7.90-11.0)	9.20 (8.0-9.80)	0.20	0.04
TSH (mIU/ml)	1.1 (.10-1.90)	1.0 (0.10-2.10)	0.50 (0.10-2.60)	1.10 (1.10-2.20)	0.30	0.40	2.0 (.60-17.0)	1.70 (0.30-17.0)	1.20 (0.20-40.0)	2.0 (1.50-16.0)	0.30	0.50
Vit D (ng/ml)	20 (17-35)	29 (25-54)	28 (11-35)	25 (16-34)	0.80	1.0	15 (8-27)	21 (10-39)	30 (16-60)	24 (21-36)	0.01	0.04

†Significant difference between time trend and parameters (Friedman test)

†Significant difference of parameters between first follow up (weeks 4) and second follow up (weeks 8) (Wilcoxon sign rank test)

[a] Values are given as median (minimum-maximum)

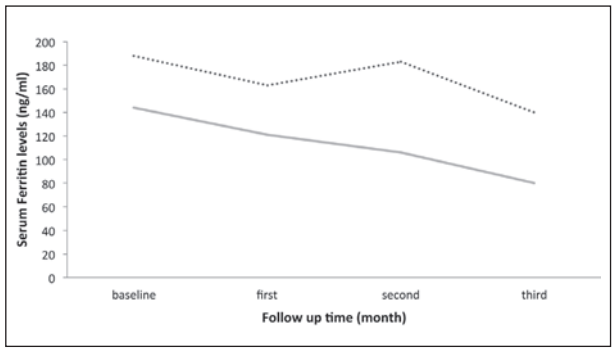

Figure 1. Ferritin levels in patients in thechloroquine group (solid line) compared to the placebo group (dotted line). There was no significant difference in the ferritins levels during 12 weeks follow up between the treatment and control groups (p-value >0.05)

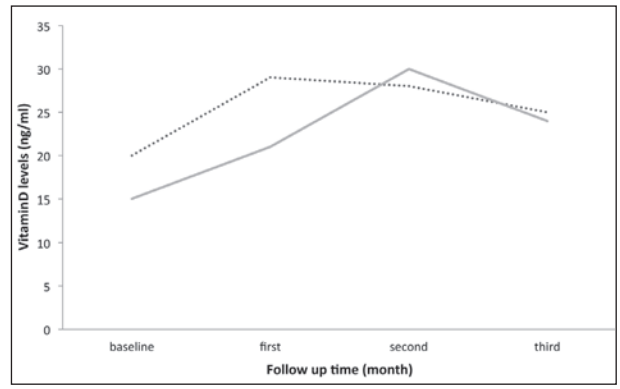

Figure 2. VitaminD levels in patients in thechloroquine group (solid line) compared to the placebo group (dotted line). There was no significant difference in Vitamin D levels during 12 weeks follow up between the treatment and control groups (p-value >0.05)

Furthermore, within the control group, significant reduction of ALT (57 to 50 and to 42 U/l) (P=0.03) and cholesterol (from 144 to 134 and to 131) (P=0.04) levels were observed between baseline and first follow-up, and between first follow-up and second follow-up (Table 2).

Thyroid function and serological levels of 25-OH vitamin D assessments

Serum TSH levels were slightly higher in the chloroquine group than in the placebo group. Furthermore, our results showed decreasing trend for T3 and T4 level in the chloroquine group in comparison to the placebo. Even though the median T3 level decreased from 1.70 to 1.40 ng/ml (P-value=0.05), and T4 from 11 to 10 micg/dl (P-value=0.04) in the chloroquine group, a similar decrease was observed in the control group (Table 2).

Results showed a significant increase in vitamin D levels from baseline to the second follow up (week 8) in the chloroquine group, rising from 15 to 34 ng/ml (P-value=0.04) (Table and Figure 2).

Discussion

Chloroquine is a well-known inhibitor of autophagic protein degradation and is often used as an anti-malarial, Lupus Erythematous and Arthritis Rheumatoid agent (21). Since chloroquine is known as one of the inexpensive and safe drugs, we assessed it as a new anti-HCV treatment option. To the best of our knowledge, this is the first trial designed to evaluate the effect of chloroquine for non-response patients with chronic HCV.

Our results showed the effect of chloroquine on serum AST, ALT, TG, cholesterol and ferritin profiles. The levels of the mentioned parameters decreased with treatment. ALT, AST and ferritin were indicators of liver inflammation. The AST and ALT showed significant positive correlation from baseline to 4^{th} and 8^{th} weeks of treatment, with serum ferritin showing significant positive correlation from baseline to 4^{th}, 8^{th} and 12^{th} weeks of treatment. Also, the serum ferritin had a significant decrease during treatment compared with the placebo. This result corresponds with the previous literature (9, 22). Thus, ferritin may be a good indicator of inflammatory status in chronic hepatitis patients before and during treatment.

Ferritin is the major cellular storage protein for iron. In normal people, elevated serum ferritin is associated with an increase in total body iron stores. In inflammation, the source of the elevated ferritin is thought to be secretion by the reticuloendothelial cells. In liver abnormality, injury to the hepatocytes causes release of ferritin into the circulation (22). Therefore, decreased ferritin status may improve the efficacy of treatment.

With chloroquine therapy, Vitamin D levels increased. A previous study proposes interplay between

the hepatic vitamin D endocrine system and HCV, suggesting that vitamin D has a role as a natural antiviral mediator(13). Importantly, our study implies that chloroquine might have a vitamin D-sparing effect, thus improving antiviral treatment of HCV-infected patients (12, 14).

In HCV patients without thyroid diseases and with normal thyroid function, higher TSH serum levels and a higher hepatic expression of TSH were associated with severe fibrosis, suggesting a profibrogenic role of TSH in the liver, through a different mechanism(17-19). Waist-to-hip-ratio in adults correlates with central (visceral) obesity and has been shown to be more accurate than BMI in predicting cardio metabolic risk factors in adults. In the present study, a decrease in WC (and thus central obesity) in the intervention group was observed, indicating an important risk reduction with regard to cardio metabolic diseases and non-alcoholic fatty liver disease.

Furthermore, the decrease in the levels of these factors was related to the duration of treatment. After chloroquine was discontinued at the end of treatment, the status of parameters had increased at the last follow up. With regard to safety, no unexpected adverse events were observed in our study, and the rate of premature discontinuation was almost zero.

Like other studies, the present study had some limitations, with the main one being the small sample size. Due to the small number of patients, we were not able to demonstrate statistical significance in our primary end point results, nor could the role of variables such as age and histological or biochemical findings be clarified. Reasons for the limited aim are the highly focused patient group, as well as the strict inclusion and exclusion criteria. The small sample size limits the conclusions to be drawn; nevertheless our results demonstrated the clinical response and decrease in the levels of the mentioned parameters through chloroquine therapy during the treatment regimen duration. We achieved these results despite selecting genotype 1 which is more resistant to treatment (23). In summary, these results are useful for gaining insight into the feasibility of a new horizon for HCV therapy. This pilot trial encourages further studies which explore the effectiveness of chloroquine treatment in non-response HCV patients with any genotype (24).

Conclusions

The results of this pilot trial suggest that chloroquine therapy may provide a new, effective, safe and economical therapeutic option for HCV treatment in non-response patients, and help to normalize some biochemical, ferritin and vitamin D status. Prospective randomized trials should be undertaken to evaluate this new strategy using this old drug in a large number of patients with HCV. When adding these results to our previous results (20), we conclude that Chloroquine may have an important role in treating on patients with HCV, and that autophagic proteolysis might be a new therapeutic target on the replication of HCV.

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