Original Article APMC-329

Comparison of Role of Zinc Supplementation Versus Placebo in Patients with HCV Related Cirrhosis

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Submitted for Publication
16-08-2016
Accepted for Publication
03-10-2016

ABSTRACT

Objectives: To compare Zinc supplementation in HCV related cirrhosis with placebo in terms of mean change in levels of patients HCV viral load. **Design:** Randomized controlled trial (RCT). **Setting:** Department of Medicine Allied Hospital, Faisalabad. **Period:** From August 2014 to November 2014. **Methodology:** A total of 120 cases (60 in each group) were included in the study. The patients in study group received 150 mg of elemental Zinc (Syp. Zincate-OK 20 mg/5ml containing 20 mg of elemental zinc) two times in a day with routine treatment protocol of cirrhosis and patients in control group received routine treatment of cirrhosis and placebo in the form of multivitamin. Patients were followed for 4 months. Outcome after zinc supplementation was measured in terms of mean viral load of patients from baseline (at time of admission) by PCR technique. **Results:** In our study, majority of the patients in both groups were between 41-50 years i.e. 36.67%(n=22) in Cases and 31.67%(n=19) in controls, mean and SD was calculated as 43.65+4.21 in cases and 45.27+3.98 years in controls, 61.67%(n=37) in cases and 68.33%(n=41) in controls were male and 38.33%(n=23) in cases and 31.67%(n=19) in controls were females, mean viral load at the time of admission was recorded as 51.43$\pm$23.54 in cases and 52.21$\pm$17.46 in controls, p value was 0.28 which shows insignificant difference in both groups, while mean viral load after treatment was calculated as 6.22$\pm$2.13 in cases and 28.34$\pm$5.95 in controls, p value was computed as 0.000, which shows a significant difference in both groups. **Conclusion:** We concluded that on comparison of Zinc supplementation in HCV related cirrhosis with placebo in terms of mean change in levels of patients HCV viral load, patients treated with Zinc supplementation had significantly lower viral load which suggests use of zinc supplementation in future in patients with HCV related cirrhosis.

Keywords: Hepatitis C virus, zinc supplementation, viral load.

Article Citation: Siddique A, Ahmad N, Gani K. Comparison of Role of Zinc Supplementation Versus Placebo in Patients with HCV Related Cirrhosis. APMC 2016;10(4):252-256.

INTRODUCTION

Cirrhosis of liver due to hepatitis C virus (HCV) is a very common disease which is characterized by diffused hepatic fibrosis and nodular formation.[1]

According to current global estimation approximately 175 million people are infected with HCV[2], 27% patients developed cirrhosis of liver[3] and HCV play an important role in the pathology of Hepatocellular carcinoma.[4] Reported prevalence of HCV in blood donors in Pakistan 1.18% to 7.5%.[5]

Liver plays an important role in zinc hemostasis and reduce in zinc level in cirrhosis is due to certain factors like decrease circulating levels of albumin, increase use of diuretics and poor intake. [6]

In Patients of HCV related cirrhosis with advance liver fibrosis, interferon therapy is difficult because of complications such as thrombocytopenia ad further decompensation of liver function, apart from routine treatment of HCV related cirrhosis different treatment modalities have been tried for prevention of complications of liver cirrhosis.

Low dose Zn supplementation could prevent deterioration of clinical status of cirrhosis and prevent excess Cu accumulation in non-alcoholic cirrhotic patients.[7]

The function of zinc in immune system has been studied extensively as zinc is essential both for femoral immunity and cell mediated immunity. There are many therapeutic reasons why zinc may be beneficial in the Hepatitis C treatment, including regulation of the imbalance between TH1 and TH2

cells, inhibitory effects of zinc in the HCV replicon system, antioxidant function and hepatoprotective effect of metallothionein.[8]

Furthermore, reduction in zinc levels accompanying liver cirrhosis leads to abnormal level of ammonia which precipitates hepatic encephalopathy.[9]

Different studies conducted worldwide suggest that zinc administration decreases viral load in HCV related cirrhosis and some studies also show that zinc therapy in cirrhosis due to HCV prevents hepatic encephalopathy.[9] Recent study in Japan showed viral load in patients having HCV related cirrhosis after 4 month of oral zinc supplementation is 22.9±42.5 as compared to those without oral zinc supplementation that is 4.1±29.6.[10]

The aim of this study was to prove the Zinc as an important supportive mineral in HCV related cirrhotic patients and this may help in reducing the morbidity if added to routine treatment protocol.

METHODOLOGY

Setting: This was a Randomized control trial study.

Place of study: Department of Medicine, Allied Hospital Faisalabad.

Period: Four months from August 2014 to November 2014.

Methods: 120 patients having age between 20 to 65 years of both genders diagnosed as having HCV related cirrhosis of liver (presenting with clinical signs of splenomegaly, ascites, lab investigations showing prolongation of PT (more than 3 sec. compared to normal value taken as 14 sec.) and reversed albumin to globulin ratio (less than 1.2 mg/dl and ultrasound showing any two of following coarse echo-pattern changes and nodular formation, splenomegaly, ascites) were selected from medical OPD. Patient having cirrhosis due to other common causes like hepatitis B virus, alcohol induced cirrhosis. auto-immune hepatitis were excluded from the study. After getting permission from hospital ethical review committee, Punjab Medical College, Faisalabad and taking informed written consent, patients were divided in to study group (A) and control group (B) randomly by using computer generated random number table.

The patients in study group received 150 mg of elemental Zinc (Syrup Zincate-OK 20 mg/5ml containing 20 mg of elemental zinc) two times in a day after breakfast and after lunch with routine treatment protocol of cirrhosis i.e. Syrup. Lactulose, tab, Carvidall, cap. Omeprazole, tab. Aldactone, and patient in control group received routine treatment of cirrhosis and placebo in the form of multivitamin. The rest of the management in both groups was done as per routine protocol for the management of cirrhosis. 5cc of blood sample was sent to hospital pathology lab. for estimation of viral load by PCR technique and reports verified by hospital pathologist, and followed up of the patients for 4 months carried out by his/her contact number and data was collected.

The results were entered and analyzed on SPSS version 19. Qualitative variable like gender was calculated through frequency and percentage. Quantitative variable like age of the patient and HCV viral load at time of admission and at 4 months follow up was presented by mean and standard deviation. Paired sample t-test was used to compare viral load at time of admission with viral load at 4 month follow up time. Independent sample test was used to compare HCV viral load in both groups. P-value less than 0.05 was taken as significant.

RESULTS

A total of 120 cases were enrolled in the study Age distribution of the patients was done, which shows majority of the patients in both groups were between 41-50 years i.e. 36.67%(n=22) in Cases and 31.67%(n=19) in controls while 30%(n=18) in cases and 26.67%(n=16) in controls, 20%(n=12) in cases and 23.33%(n=14) in controls and only 13.33%(n=8) in cases and 18.33%(n=11) in controls were recorded, mean and sd was calculated as 43.65±4.21 in cases and 45.27±3.98 years in controls. (Table 1). Gender distribution of the patients was done in table No.2, where 61.67%(n=37) in cases and 68.33%(n=41) in controls were male and 38.33%(n=23) in cases and 31.67%(n=19) in controls were females. (Table 2).

Table 1: Age distribution (N=120)

Age (in years)	Cases (n=60)		Controls (n=60)	
	No. of Patients	%	No. of patients	%
20-30	8	13.33	11	18.33
31-40	12	20	14	23.33
41-50	22	36.67	19	31.67
51-65	18	30	16	26.67
Total	**60**	**100**	**60**	**100**
Mean and SD	**43.65+4.21**		**45.27+3.98**	

Table 2: Gender distribution (N=120)

Age (in years)	Cases (n=60)		Controls (n=60)	
	No. of patients	%	No. of patients	%
Male	37	61.67	41	68.33
Female	23	38.33	19	31.67
Total	**60**	**100**	**60**	**100**

Mean viral load at the time of admission was recorded as 51.43±23.54 in cases and 52.21±17.46 in controls, p value was 0.28 which shows insignificant difference in both groups. (Table No.3)

Mean viral load after treatment was calculated as 6.22±2.13 in cases and 28.34±5.95 in controls, p value was computed as 0.000, which shows a significant difference in both groups. (Table No.4)

Table 3: Mean viral load at the time of admission (n=120)

Cases	Controls
51.43±23.54	52.21±17.46

P value=0.28

Table 4: Mean viral load after treatment (N=120)

Cases	Controls
6.22±2.13	28.34±5.95

P value=0.000

DISCUSSION

Factors known to be involved in carcinogenesis from chronic liver disease include hepatitis viruses, alcohol consumption, and smoking.[11,12] In addition, several metabolic factors have recently been shown to be associated with liver carcinogenesis. Obesity and diabetes mellitus are risk factors for liver carcinogenesis,[11] and it has been suggested that iron is involved in carcinogenesis in patients with hepatitis C virus-related chronic liver disease. [13] In patients with chronic viral liver disease, antiviral therapy (e.g., interferon therapy for chronic hepatitis C and nucleic acid analog therapy for virus-related chronic liver disease) has been shown to suppress carcinogenesis; however, antiviral therapy alone cannot completely prevent liver carcinogenesis in these patients.[11] Furthermore, as was the case in this study, in hepatitis C virus-related chronic liver disease with advanced liver fibrosis, interferon therapy is often difficult because of complications such as thrombopenia. Therefore, in addition to anti-viral therapy, it is important to investigate metabolic factors that possibly suppress carcinogenesis.

It has been shown that zinc, which is a trace metal, is deficient in patients with chronic liver disease and is involved in metabolic abnormalities primarily pertaining to ammonia; these metabolic abnormalities can be alleviated by zinc replacement.[14]

We planned this study considering the fact that Zinc is an important, cheap and readily available mineral having many effects in HCV related cirrhotic patients, its role is not studied and practiced locally. The result of study may help in reducing the morbidity in cirrhotic patients if we add this mineral in addition to routine treatment protocol.

In our study, majority of the patients in both groups were between 41-50 years i.e. 36.67%(n=22) in Cases and 31.67%(n=19) in controls, mean and SD was calculated as 43.65+4.21 in cases and 45.27+3.98 years in controls, 61.67%(n=37) in cases and 68.33%(n=41) in controls were male and 38.33%(n=23) in cases and 31.67%(n=19) in controls were females, mean viral load at the time of admission was recorded as 51.43±23.54 in cases and 52.21±17.46 in controls, p value was 0.28 which shows insignificant difference in both groups, while mean viral load after treatment was calculated as 6.22±2.13 in cases and 28.34±5.95 in controls, p value was computed as 0.000, which shows a significant difference in both groups.

The findings of the study are in agreement with a recent study in Japan which showed viral load in patients having HCV related cirrhosis after 4 month of oral zinc supplementation is 22.9±42.5 as compared to those without oral zinc supplementation that is 4.1±29.6.[10]

Some demographic data may alter zinc plasma concentration in human. Lopez et al reported that Serum Zn concentrations were slightly higher in men than in women and also there is some elevated serum Zn levels in smoking men rather than nonsmokers.[15]

The results of the study are more considerable because of the effective role of the zinc supplement in pharmacotherapy of viral hepatitis. Yuasa et al. have shown that zinc may play an important role as a negative regulator of hepatitis C viral (HCV) replication in genome-length HCV RNA-replicating cells. They mentioned that zinc appears to offer a novel approach to the development of future plans for the treatment of intractable chronic hepatitis C.[16]

Himoto et al. examined the effect of polaprezinc, a complex of zinc and L-carnosine, on inflammatory activity and fibrosis in HCV infected patients. They reported that polaprezinc exerts an anti-inflammatory effect on the liver in patients with HCV-related Chronic liver disease by reducing iron overload.[17]

Zinc deficiency, common in liver disease may be partially due to decreased intake, increased losses secondary to malabsorption, increased dietary requirement and possibly a diuretic regimen.[18] Nutritional therapy including enteral nutrition, parenteral nutrition and micronutrient supplementation should be part of the multidisciplinary management of the cirrhotic patients.[19]

Based on the result of the study as well, administration of zinc may be recommended for Pakistani cirrhotic patients due to hepatitis C.

In future more studies are recommend for the role of zinc administration on clinical, pathological status and pharmacotherapy response of Pakistani cirrhotic patients due to hepatitis C.

CONCLUSION

We concluded that on comparison of Zinc supplementation in HCV related cirrhosis with placebo in terms of mean change in levels of patients HCV viral load, patients treated with Zinc supplementation had significantly lower viral load which shows that Zinc supplementation may be adopted in cirrhotic patients in future.

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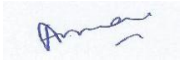
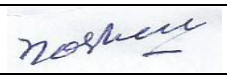
Dr. Amna Siddique	Main Author	
Dr. Nosheen Ahmad	Discussion & References	
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