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Comparison of Efficacy of Zinc Supplementation and Standard Treatment with Standard Treatment Alone in Heptic Encephalopathy

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ABSTRACT

Objective: To compare the efficacy of combination of zinc supplementation and standard treatment with standard treatment alone in patient of hepatic encephalopathy. **Study Design:** Randomized Controlled Trial. **Settings:** Medical Department, Allied Hospital, Faisalabad-Pakistan. **Duration:** Six months study from 03-08-2013 to 02-01-2014. **Methodology:** All the patients having hepatic encephalopathy fulfilling the inclusion criteria were randomly collected and were assorted in two groups each having 45 patients and assigned as group A and group B. Group A was given Zinc Sulphate 600mg in 3 divided doses for one week plus standard treatment which includes; Ceftriaxone 1g IV BD, Syrup Metronidazole 2TSF TDS, Syrup Lactulose 2TSF TDS, Group B was given standard treatment alone. Information collected was comprised of name, age, sex, address and improvement of grade of encephalopathy after one week. **Results:** 90 patients were included in the study. Mean age of study population was 51.83 ± 11.12 years. 61(67.8%) were male and 29 (32.2%) were females. Group A was given zinc sulphate and group B was given placebo. Mean age in group A was 52.96 ± 12.32. 28(62.2%) were male and 17(37.8%) were females in group A. Mean age in group B was 50.71 ± 8.38. 33(73.3%) were male and 12(26.7%) were female in group B. Chi-square test was applied to efficacy in group A and group B. (p-value 0.001) which is highly significant. **Conclusion:** It has been concluded from this study that zinc supplementation significantly improves hepatic encephalopathy in patients with liver cirrhosis.

Keywords: Hepatic encephalopathy, Zinc supplementation, Efficacy.

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INTRODUCTION

Hepatic encephalopathy is a complex neuropsychiatric syndrome in chronic liver disease which is characterized by disturbances in behavior and consciousness as well as neurological symptoms.[1] Hepatic Encephalopathy manifests by the broad spectrum of neuropsychiatric disturbances such as: defects in cognitive, emotional, behavioral, psychomotor, and locomotive functions. Hepatic Encephalopathy affects the cognitive function and quality of life of patients. The pathogenesis of hepatic encephalopathy includes hyperammonemia, imbalance between excitatory and inhibitory neurotransmission and false neurotransmitters acting on the brain.[2] Hepatic Encephalopathy is a grim outcome of chronic liver disease and it is a poor prognostic factor. Cognitive function declines reversibly in hepatic encephalopathy and can be improved and even prevented in some cases with appropriate treatment.[3] Synthetic disaccharides like lactulose,[4] nonabsorbable oral antibiotics like rifaxamin[5] and branched chain amino acids[6] are commonly used to treat hepatic encephalopathy. Zinc deficiency has been found in association with hepatic encephalopathy.[7] Poor nutritional intake caused by a protein-restricted diet, impaired intestinal absorption, and excessive urinary loss are all potential causes of a low serum zinc levels in patients with advanced cirrhosis. Short-term oral zinc supplementation may improve hepatic encephalopathy by correcting the zinc deficiency that compromises the conversion of ammonia to urea. Few small-scale studies have shown that zinc supplementation is effective in treatment of hepatic encephalopathy.[8] In one study by Takuma et al, it was shown that no. of hepatic encephalopathy grade per patient improved in 54% significantly as compared to 26% in control group.[9] Hepatic encephalopathy treatment is still a clinical problem for treating physicians and there is need for new therapeutic options. Zinc Supplementation is a relatively unexplored territory for this purpose and it holds promising results for hepatic encephalopathy treatment. This study will help us establish the effectiveness of zinc supplementation in hepatic encephalopathy and to make necessary recommendations regarding its clinical use.

METHODOLOGY

Study Design: Randomized Controlled Trial.
Settings: Department of Medicine, Allied Hospital, Faisalabad-Pakistan
Duration: 6 months from 03-08-2013 to 02-01-2014.
Inclusion Criteria: All the patients age ranges from 18 to 70 years of both genders, and hepatic encephalopathy grade III & IV due to liver cirrhosis were included.

Exclusion Criteria: All the patients having previous history of Zinc Hypersensitivity, pregnancy, lactating mother, Uraemic encephalopathy, Meningitis or encephalitis as assessed clinically, atypical Pneumonia and hypoglycemia were excluded.

Methods: Approval from hospital Ethical Review Committee was taken after formulation of synopsis. 90 Patients fulfilling the inclusion criteria were enrolled in the study. Informed consent was taken from each participant of the study. Patients were divided into two groups (group A and group B) by using computer generated random number table. Group A was given zinc sulphate 600mg in three divided doses per day for one week plus standard treatment. Group B was given standard treatment alone for one week. Information collected comprised of age, sex, address, contact number, improvement in grade of hepatic encephalopathy assessed clinically after 1 week. Data was collected through self-conducted interviews using a standardized proforma. Efficacy was measured in terms of improvement in grade of hepatic encephalopathy. Improvement was considered if there was at least one level decline in grades of hepatic encephalopathy. All the collected information transferred to SPSS version 20 and analyzed accordingly. Mean and standard deviation was calculated for all quantitative variables like age. Frequency and percentage were calculated for all qualitative variables like gender, grade of hepatic encephalopathy at baseline and after one week. Chi square test was applied to compare efficacy for both groups. P value of <0.05 was considered as significant

RESULTS

90 patients were included. Mean age of study population was 51.83 ± 11.12 years. Group A was given zinc sulphate and group B was given placebo. Mean age in group A was 52.96 ± 12.32. 28(62.2%) were male and 17(37.8%) were females in group A. Mean age in group B was 50.71 ± 8.38. (table 1)

Table 1: Age distribution

Statistics			
Age	ALL	Group A	Group B
n	90	45	45
Mean	**51.83**	**52.96**	**50.71**
Std. Deviation	**11.12**	**12.32**	**8.38**

Chi-square test was applied to efficacy in group A and group B. (table 2) (p-value 0.001) which is highly significant.

Table 2: Efficacy according to treatment group

Efficacy	Treatment Group		Total	p-value
	Group A	Group B		
Yes	25	10	35	0.001
No	20	35	55	
Total	45	45	90	

Table 3: Efficacy according to treatment gender

Efficacy	Gender		Total	p-value
	Male	Female		
Yes	25	10	35	0.362
No	36	19	55	
Total	61	29	90	

Table 4: Efficacy according to treatment age group

Efficacy	Age groups			Total	p-value
	18-40	41-60	61-80		
Yes	3	25	7	35	0.740
No	3	38	14	55	
Total	6	63	21	90	

Table 5: Efficacy according to treatment grade of HE

Efficacy	Grade of Hepatic Encephalopathy at presentation		Total	p-value
	Grade 3	Grade 4		
Yes	22	13	35	0.362
No	32	23	55	
Total	54	36	90	

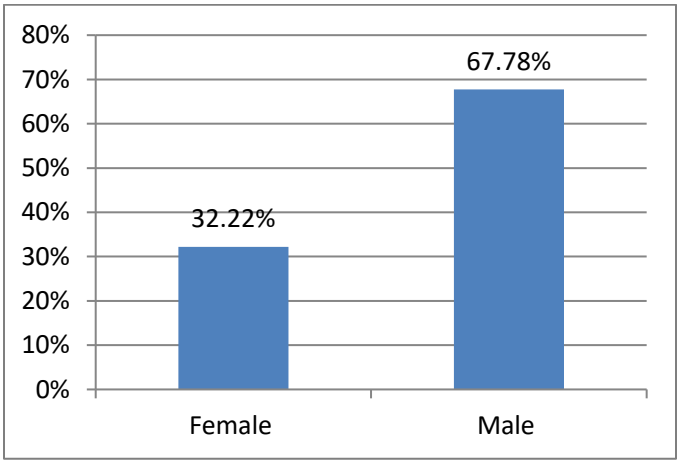

Figure 1: Gender of patients

61(67.8%) were male and 29 (32.2%) were females (Figure 1).

DISCUSSION

Liver Cirrhosis is a very common problem with a significant impact on Health-related Quality of life especially in patients with hepatitis C virus infection. Hepatic encephalopathy is one of the most disabling complications of Liver cirrhosis that affect the quality of life of liver cirrhosis patients. Cirrhosis is end stage liver disease where normal liver parenchyma is replaced by regenerating nodules and scar tissue resulting from a variety of causes including viruses like HBV, HCV, HDV, alcoholic liver disease, PBC, Wilson disease, haemochromatosis, alpha-1 antitrypsin deficiency, autoimmune hepatitis and others. Hepatic Encephalopathy complicates 27% of patients with liver cirrhosis

at some point in time and it has got a high mortality. Treatment options available for hepatic encephalopathy include lactulose (oral and enema preparations), rifaximin, neomycin, metronidazole, branched chain amino acid, SARS, flumazenil. Some of these treatments are part of the guidelines and others are still controversial for use in hepatic encephalopathy. But response to this treatment is unpredictable and physicians are always desperate to find new treatment strategies for treatment of hepatic encephalopathy. Zinc supplementation is an emerging treatment option and has been showing promising results in recent trials. We conducted a small study over a period of six months duration on role of zinc supplementation in hepatic encephalopathy and compared the results with standard treatment alone. We enrolled a total of 90 patients divided into group A and group B. Zinc supplementation improved hepatic encephalopathy in 55.55% patients as compared to standard treatment group in which improvement occurred in only 22% patients (p-value 0.0000).

There has been a lot of research in the past on zinc deficiency in hepatic encephalopathy and its role in its pathogenesis. Schliess F et al studied the role of zinc in pathogenesis of zinc deficiency and its supplementation in patients with overt hepatic encephalopathy. He described that Ammonia plays a key role in the pathogenesis of hepatic encephalopathy by inducing astrocyte swelling and/or sensitizing astrocytes to swelling by a heterogeneous panel of precipitating factors and conditions. Astrocyte swelling produces reactive oxygen and nitrogen oxide species (ROS/RNOS), which again increase astrocyte swelling, thereby creating a self-amplifying signaling loop. Astroglial swelling and ROS/RNOS increase protein tyrosine nitration and may account for neurotoxic effects of ammonia and other precipitants of hepatic encephalopathy. An elevation of [Zn (2+)] (i) mediates mRNA expression of metallothionein and the peripheral benzodiazepine receptor (PBR) induced by hypoosmotic astrocyte swelling. Zinc supplementation reduces the toxic effects of ammonia and improves hepatic encephalopathy.[9] Shaposhnikova NA et al described the beneficial effects of oral zinc treatment in patients with hepatic encephalopathy. He also described that diuretic therapy with spironolactone and frusemide for treatment of ascites due to portal hypertension results in loss of zinc in urine and this deficiency contributes towards pathogenesis of hepatic encephalopathy. Zinc supplementation results in significant improvement in symptoms of hepatic encephalopathy which supports the results of our study in which zinc supplementation has also been found very beneficial.[10] Chetri K et al described that in animal experiments, zinc supplementation leads to a reduction in blood ammonia. Zinc is an essential trace element and functions as an antioxidant. Zinc deficiency also leads to alteration of neurotransmitters like gamma aminobutyric acid and norepinephrine.[11]

Chavez-Tapia et al studied zinc supplementation in 233 patients. He reported that zinc supplementation is associated with significant improvement in hepatic encephalopathy but there is no reduction in hepatic encephalopathy recurrence and rate of hospitalization.[12] This supports the results of our study for zinc supplementation.

Pitfalls of my study include:

CONCLUSION

It has been concluded from this study that zinc supplementation significantly improves hepatic encephalopathy in patients with liver cirrhosis. Zinc supplementation can be safely recommended for treatment of hepatic encephalopathy in routine. It is recommended that zinc supplementation should be made part of recommendations for treatment of hepatic encephalopathy.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

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