

Oral Zinc Supplementation as an Adjunct Therapy in the Management of Hepatic Encephalopathy: A Randomized Controlled Trial

Marcus R. Pereira

A. Study Purpose

Hepatic encephalopathy is a common complication in patients with liver disease, ranging from subtle abnormalities detectable only by psychometric testing to deep coma. Although a sign of advanced disease, most episodes of hepatic encephalopathy are readily reversible with medical treatment. Once the acute event is treated, the goal of chronic management for these patients is, among other things, the prevention of further episodes of hepatic encephalopathy. Currently, standard therapy involves the combination of lactulose (titrated to at least 2 bowel movements a day) and a diet that is restricted to 0.8 g/kg, or about 60 grams, of protein a day. Although efficacious, this regimen is inconvenient and difficult, and therefore prone to poor compliance.

Many adjunct therapies have been proposed, including branched chain amino-acids, benzodiazepine receptor antagonists (such as flumazenil), and antibiotics (neomycin, rifaximin). Zinc supplementation has also been studied in this setting. Previous studies have found that zinc is essential in the metabolism of ammonia in the body. Two of the five enzymes responsible for the urea cycle are zinc-dependent, as is muscle glutamine synthetase, an enzyme involved in the conversion of ammonia into glutamine. Furthermore, zinc deficiency is common in patients with advanced liver disease. This is likely multifactorial, including poor dietary intake, impaired intestinal absorption and excessive urinary losses secondary to the use of diuretics.

Previous studies on zinc supplementation have revealed conflicting information. While a recent controlled trial revealed that 3 month zinc supplementation showed a significant improvement in psychometric test scores in eight patients with advanced liver disease, earlier studies, including a long term randomized controlled trial, did not show any significant difference. Most current reviews on chronic management of hepatic encephalopathy conclude that there is not enough evidence to assess the efficacy of zinc supplementation in this patient population and that further studies should be carried on.

The overall purpose of this study is to determine the efficacy of zinc supplementation as an adjunct therapy in the prevention of hepatic encephalopathy in patients with advanced liver disease.

B. Study Design and Statistical Analysis

This prospective, randomized, stratified, controlled and double blinded study will evaluate the efficacy of zinc supplementation as an adjunct therapy to lactulose and protein restricted diet in patients with liver disease complicated by hepatic encephalopathy. In order to account for the different levels of severity in liver disease, eligible subjects will be stratified into three groups based on their Child-Pugh Class, a classification system for severity of liver disease that ranges from A/mild to C/severe.

Parameter	Points assigned		
	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin, mg/dL	≤ 2	2-3	>3
Albumin, g/dL	>3.5	2.8-3.5	<2.8
Prothrombin time			
Seconds over control	1-3	4-6	>6
INR	<1.7	1.8-2.3	>2.3
Encephalopathy	None	Grade 1-2	Grade 3-4

Child-Pugh classification of severity of liver disease Modified Child-Pugh classification of the severity of liver disease according to the degree of ascites, the plasma concentrations of bilirubin and albumin, the prothrombin time, and the degree of encephalopathy. A total score of 5-6 is considered grade A (well-compensated disease); 7-9 is grade B (significant functional compromise); and 10-15 is grade C (decompensated disease). These grades correlate with one- and two-year patient survival: grade A – 100 and 85 percent; grade B – 80 and 60 percent; and grade C – 45 and 35 percent.

Source: uptodate.com

Once study subjects are equally stratified in three groups, they will be randomized into 2 groups: a) the experiment group will receive standard therapy plus 6 months of zinc sulfate 200 mg orally three times a day, b) the control group will receive standard therapy plus placebo pills identical to the zinc pills three times a day for 6 months. All other medically necessary medications will be continued. The randomization will be masked to the investigational team until all data is collected and ready to be analyzed.

For the purpose of calculating sample size, we will use previously published data on zinc supplementation and its effects on the number connection test (to be further described below), which showed an improvement from a mean of 86 seconds on the control group to 62 seconds on the experiment group, with a standard deviation of 40 seconds. Assuming a similar effect, we would need 45 patients in each arm to achieve 80% power and a type I error of 0.05. However, assuming a drop out rate of approximately 20%, we would need 10 additional subjects to each arm for a total of 55 in the placebo groups and 55 patients in the experiment group.

The primary outcome in this study will be performance in the two most widely used psychometric tests: the number connection test (NCT) and the continuous reaction time to sound (CRTs). These tests have been reliably used in previous studies as highly sensitive tests in the grading of hepatic encephalopathy. Additionally, this study will collect data on recurrence of hepatic encephalopathy, severity of encephalopathic episodes and liver function tests.

C. Study Procedure

This entire study will likely last two years with an anticipated duration of six months for each patient enrolled. Patients will be followed on a monthly basis in the Liver Clinic at CPMC. Each month, for a total of six visits each patient, patients will be assessed, along with usual routine exam, for the degree of hepatic encephalopathy, if any. They will undergo an NCT and CRTs as well as be analyzed for their liver function tests and zinc level. As a measure of safety, given the low risk of neutropenia, patients will have a complete blood count with differential drawn during each visit as well. In order to evaluate compliance with their standard therapy, patients will be asked keep a diary of daily bowel movements as well as a food intake diary for the duration of the study.

GRADE	LEVEL OF CONSCIOUSNESS	PERSONALITY AND INTELLECT	NEUROLOGIC SIGNS	ELECTROENCEPHALOGRAPHIC ABNORMALITIES
0	Normal	Normal	None	None
Subclinical	Normal	Normal	Abnormalities only on psychometric analysis	None
1	Inverted sleep pattern, restlessness	Forgetfulness, mild confusion, agitation, irritability	Tremor, apraxia, incoordination, impaired handwriting	Triphasic waves (5 cycles/sec)
2	Lethargy, slow responses	Disorientation as regards time, amnesia, decreased inhibitions, inappropriate behavior	Asterixis, dysarthria, ataxia, hypoaactive reflexes	Triphasic waves (5 cycles/sec)
3	Somnolence but rousability, confusion	Disorientation as regards place, aggressive behavior	Asterixis, hyperactive reflexes, Babinski signs, muscle rigidity	Triphasic waves (5 cycles/sec)
4	Coma	None	Decerebration	Delta activity

Source: Riordan et al

D. Study Drugs

For this study, oral zinc sulfate will be used as the study drug. It is approved for treatment of zinc deficiency. The standard dosage of zinc sulfate 200 milligrams orally three times a day will be used in this study. This provides the usual recommended daily allowance of 25 to 50 mg of elemental zinc daily (2.5-4 mg/kg/day). Zinc sulfate is safe and has generally been well-tolerated in previous studies. Most common adverse effects include nausea/vomiting and diarrhea. Neutropenia is a more serious adverse effect that has been reported in patients who significantly overdose in zinc (>600 mg of elemental zinc a day).

E. Medical Device

This study will not utilize investigational devices.

F. Study Questionnaires

This study will include two questionnaires, a food frequency and a bowel movement frequency that will be completed on a monthly basis and submitted at each clinic visit. The collection of this data will be used to control for differences in the standard therapy (protein controlled diet and minimum of 2 bowel movements a day) given to both study groups.

G. Study Subjects

Subjects will be patients 18 years of age or older who meet inclusion criteria and do not have exclusion criteria.

1. Inclusion criteria include:
 - a) Histologically documented cirrhosis within 2 years,
 - b) Cirrhosis secondary to Hepatitis C or alcohol,
 - c) At least one documented episode of hepatic encephalopathy during admission,
 - d) Abstention form alcohol or other illicit drugs for the past year,
 - e) patient stable to be discharged with plans to follow up in liver disease clinic.
2. Exclusion criteria include:
 - a) Continued drinking of alcohol,

- b) Hepatocellular carcinoma,
- c) No plans to follow up in liver disease clinic,
- d) Absolute Neutrophil Count < 1000.

G. Recruitment of Subjects

Patients will be recruited at New York Presbyterian Hospital - Columbia University Medical Center. Subjects will be identified by residents, fellows, and attendings on hospital floors. . However, subjects will only be approached if primary attending physician agrees to enrollment in the study. Once the subject and his/her physician agree to participate, a study investigator will obtain informed consent from the subject.

H. Confidentiality of Study Data

All study patient files will be coded and kept confidential in a password protected in a laptop computer accessible only to members of the investigational team.

I. Potential Conflict of Interest

The author has no proprietary interest in the therapy under investigation.

J. Location of the Study

This study will be carried out at New York-Presbyterian Hospital, Columbia University Medical Center and its associated Liver Clinic.

K. Potential Risks

The medical risk in this study is minimal to none. All subjects will be receiving standard medical therapy that is FDA approved, including zinc sulfate. The major risk of zinc sulfate comes in the setting of extremely high doses. Therefore, patients will be required to stop taking multivitamin supplements that could remotely cause high intake of zinc. They will be educated on the risks of taking high levels of zinc. As an added measure of safety, patients will have a complete blood count with differential and zinc level drawn at each clinic visit.

L. Potential Benefits

Potential benefits have been outlined above but include improved performance on psychometric tests, fewer episodes of hepatic encephalopathy as well as improved overall liver function tests.

M. Alternative Therapies

The study does not involve experimental therapies since zinc sulfate is already approved used for this use.

N. Compensation to Subjects

Patients will not receive any form of compensation for participating in this study.

O. Costs to Subjects

There will be no extra costs to subjects. Zinc sulfate, or placebo will be provided to patients.

P. Minors as Research Subjects

Only adults over 18 years of age will be screened for this study.

Q. Radiation or Radioactive Substances

No radiation will be administered a part of this study.

R. References

1. Reding et al "*Oral zinc supplementation improves hepatic encephalopathy. Results of a randomized controlled trial.*" Lancet 1984 Sep 1; 2(8401): 493-5.
2. Bresci et al. "*Management of hepatic encephalopathy with oral zinc supplementation: a long term treatment.*" Eur J Med. 1993 Aug-Sep;2(7): 414-6
3. Marchesini et al. "*Zinc supplementation and amino acid-nitrogen metabolism in patients with advanced cirrhosis.*" Hepatology 1996; 23: 1084-92.
4. Riggio et al "*Short-term oral zinc supplementation does not improve chronic hepatic encephalopathy. Results of a double-blind crossover trial.* Dig Dis Sci. 1991 Sep;36(9): 1204-8.
5. Riordan et al "*Treatment of hepatic encephalopathy.*" NEJM. 1997 Aug;337(7): 473-9.
6. Van Der Rijt et al. "*Overt hepatic encephalopathy precipitated by zinc deficiency.*" Gastroenterology 1991;100:1114-8.
7. Conn et al. "*Trailmaking and number connection tests in the assessment of mental state in portal systemic encephalopathy.*" Am J Dig Dis 1977; 22:541.