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Effect of zinc on liver cirrhosis with hyperammonemia: A preliminary randomized, placebo-controlled double-blind trial

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ABSTRACT

Objective: To our knowledge, no randomized study has shown whether zinc replacement therapy is effective for hyperammonemia in liver cirrhosis; therefore, we performed a double-blind, placebo-controlled trial to examine efficacy and safety of the zinc replacement therapy.
Methods: Patients with liver cirrhosis and hyperammonemia (at or above the institutional reference value) and hypozincemia (≤65 μg/dL) were enrolled in the outpatient units of the participating institutions and were randomly divided to receive placebo (P group) or zinc acetate preparation at a dose of 3 capsules/d for a total zinc content of 150 mg/d (Z group) by the envelope method. Of the 18 enrolled patients, 6 dropped out; thus, the analyses included 12 patients (5 in the P group and 7 in the Z group). Variations in blood concentrations of zinc and ammonia as well as liver function test results were compared.
Results: Blood zinc levels significantly increased in the Z group ($P = 0.0037$; Friedman test) but not the P group. Blood ammonia levels significantly decreased in the Z group ($P = 0.0114$; Friedman test) but not the P group. The percent change in blood ammonia level also revealed significant reduction at the eighth week in the Z group ($P = 0.0188$: Mann-Whitney test). No serious adverse events attributable to the zinc preparation were noted.
Conclusion: Although this study is preliminary and includes a small sample, it is, to our knowledge, the first randomized controlled trial to show that zinc supplementation for 3 mo seems effective and safe for treating hyperammonemia in liver cirrhosis. Studies with a larger sample size are needed to confirm our findings.

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Introduction

Protein-energy malnutrition in patients with liver cirrhosis can degrade their prognoses for survival and cause complications such as hepatic encephalopathy [1–6]. The effectiveness of several nutritional interventions on nutritional and metabolic abnormalities associated with liver cirrhosis has been described. The administration of branched-chain amino acids improves protein metabolism, reducing the incidence of complications and improving prognosis for survival [7–9]. Additionally, consuming foods divided more than three times per day can improve abnormal energy metabolism [10]. Thus, the management of nutritional factors is clinically important when treating liver cirrhosis. Recently, among various nutrients, trace metals such as iron and zinc were found to be closely involved in the pathophysiology of liver cirrhosis [11–14]. To date, however, the mechanisms underlying their metabolism and pathologic significance have not been clarified.

Zinc plays an indispensable role in cell growth and differentiation and is very important for metabolism in humans [15]. More than 300 proteins contain domains with zinc, and these domains are important for regulating cellular functions [16–19]. Therefore, it is likely that zinc is closely involved in many bodily functions. The homeostasis of zinc in vivo is primarily preserved by a balance between the zinc-binding protein metallothionein and the expression of two zinc transporters [20–24]. If zinc stores become deficient, numerous problems, including growth disorder, cognitive disorder, and compromised immune function, can occur [25–28]. Zinc deficiency is likely to occur in patients with liver cirrhosis, and factors that are potentially responsible for such deficiency include disturbed zinc absorption by the digestive tract and increased zinc excretion in the urine [12,13]. Furthermore, diuretics, which are commonly used to treat edema and ascites, aggravate zinc deficiencies in patients with liver cirrhosis by increasing zinc excretion in the urine [29].

It has been suggested that zinc deficiency is related to the pathogenesis of hepatic encephalopathy. Several studies have shown a statistically significant inverse relationship between the serum levels of zinc and ammonia [30–32]. On the basis of these findings, several studies have examined the effects of zinc supplementation in patients with hyperammonemia [30,33–36]. Although two randomized controlled trials (RCTs) have been performed to examine these effects, the period of zinc supplementation in these trials was rather short (8 and 10 d), and the results were controversial [33,37]. One study showed that longer supplementation (3 mo) of zinc in patients with hepatic encephalopathy reduced serum ammonia levels and increased plasma urea levels, but this was not an RCT [14]. The main effects of zinc supplementation on ammonia metabolism proposed thus far are increased ammonia uptake of the muscle through activation of glutamine synthetase and increased activity of ornithine transcarbamylase, a key enzyme of the urea cycle in the liver [13]. Liver ornithine transcarbamylase activity was found to decrease in zinc-deficient rats, leading to increased plasma ammonia, whereas it significantly increased in zinc-supplemented cirrhotic rats compared with the control group [34].

In this study, we describe the results of a multicenter, placebo-controlled, double-blind randomized trial of zinc administration for 3 mo in patients with liver cirrhosis and hyperammonemia.

Methods

Participants

Between September 2009 and January 2012, patients who met the following criteria were enrolled at each institution: liver cirrhosis diagnosed by clinical symptoms, imaging studies, or histologic examination; blood ammonia level higher than the institutional reference value confirmed at least twice from blood samples collected within 2 mo before enrollment; hepatic encephalopathy grade $\leq$1 (grade 0, no symptoms; grade 1, the presence of euphoria or depression, mild confusion, slowness, or disordered sleep; grade 2, lethargy or moderate confusion; grade 3, marked confusion or sleeping almost all day; grade 4, coma) [38]; serum zinc concentration $\leq$65 μg/dL; age $\geq$20 y; and able to attend outpatient treatment. The exclusion criteria were as follows: hepatic encephalopathy grade $\geq$3; liver failure due to fulminant hepatitis; malignant disease requiring treatment during the period of the clinical trial; hospitalization required for cardiac, renal, or pancreatic disease; serious hematologic or cerebrovascular disorder; allergy to zinc preparations; and ineligibility for other reasons according to their attending doctors.

Protocol

The enrolled patients were randomly assigned to either the placebo (P) group or the zinc (Z) group by the envelope method, and the severity of hepatic insufficiency was thereafter diagnosed using hematologic tests including blood ammonia concentration and clinical symptoms, at 1-mo intervals for 3 mo. Patients assigned to the Z group took a single oral zinc acetate capsule (Nobelzin capsules, 50 mg: each capsule contains 167.84 mg zinc acetate dihydrate including 50 mg of zinc; Nobelpharma Co., Ltd., Tokyo, Japan) after each meal three times a day. Those assigned to the P group took one oral placebo capsule (identical to the zinc acetate capsule in color and form) three times a day. The adherence rates were $\geq$80% in all patients. In the safety assessment, adverse events (AEs) during treatment were observed at 1-mo intervals and severity was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4).

Statistical analysis

The Friedman test was performed to determine whether there were changes at 1-mo intervals from the start to 3 mo after the start of treatment. The Mann-Whitney test was used to analyze the differences between groups before and at each time point during the study. The χ^2 test was performed to analyze the judgment by the attending doctors about treatment efficacy.

Clinical trial registration and ethical review

This clinical trial was registered at the University Hospital Medical Information Network in June 2009 (registration no. UMIN000002402). The trial was approved by the hospital's ethical review board (no. 0909091063). The details of this trial were fully explained to each patient in oral and written form, and written consent was obtained.

Results

Analysis set

Eighteen patients who met the inclusion criteria at each institution were enrolled and assigned to either the P group (n = 8) or the Z group (n = 10) (Fig. 1). One patients in the P group dropped out of the study due to general fatigue and another due to development of liver cancer requiring treatment. These two patients were thus excluded from the analysis. Because the patient who developed liver cancer had received treatment for hepatocellular carcinoma before this trial, the liver cancer was assumed to be recurrence. In the Z group, one patient was admitted with bronchopneumonia and one patient developed dizziness and requested discontinuation of the trial despite mild symptoms. Treatment was discontinued in a third patient due to the aggravation of hepatic encephalopathy. These three patients were excluded from the analysis. Thus, the analysis ultimately included five patients in the P group and seven in the Z group. Patients' baseline characteristics are shown in Table 1. Although no significant differences in age, sex, liver function, or