INTRODUCTION

Muscle cramps are painful asymmetrical muscle contractions that can last from several seconds to minutes.1 Occurring in only about one-third of healthy adults, muscle cramping is common in hemodialysis patients; patients with severe dehydration and chronic illnesses, such as motor neuron and thyroid diseases; and patients taking medications, such as diuretics. Liver cirrhosis (LC) patients are especially vulnerable to painful muscle cramps and constitute 51–88% of the overall prevalence of muscle cramps.2,3 Interestingly, research has shown that between cirrhotic patients and patients with other diseases (e.g., heart failure) necessitating the consumption of the same doses of diuretics, the frequency of muscle cramps was higher in cirrhotic patients than in the other patients. Accordingly, muscle cramps are considered as cirrhotic complications.4-6

In cirrhotic patients, although muscle cramping is significantly associated with a lower quality of life,7,8 it is usually overlooked by physicians, as these patients face more life-threatening complications, such as ascites, variceal bleeding, or encephalopathy. As such, the pathophysiology of muscle cramps remains not well-established. Early studies have revealed that the frequency of muscle cramps increases as a patient’s hepatic func-

Effectiveness of 4-Week Oral Taurine Treatment for Muscle Cramps in Patients with Liver Cirrhosis: A Single-Arm Pilot Study

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Purpose: Painful muscle cramps are a common complication in liver cirrhosis patients, and no effective treatment is available. This pilot study aimed to evaluate whether taurine supplementation improves muscle cramps in Korean cirrhotic patients.

Materials and Methods: Ten cirrhotic patients who experienced muscle cramps one or more times/week were enrolled in this prospective single-arm study and administered with an oral taurine solution (1 g/50 mL) thrice a day for 4 weeks. Taurine was discontinued for the subsequent 4 weeks. The frequency and intensity of muscle cramps were evaluated using a questionnaire at weeks 0, 2, 4, 6, and 8 after the start of treatment.

Results: At baseline, the median frequency of muscle cramps was six times/week, and all patients had severe pain. Muscle cramp scores (frequency×intensity) decreased in seven patients by weeks 4 and 8 after treatment initiation. Compared to baseline muscle cramp scores [median 21, interquartile range (IQR): 8–84], median muscle cramp scores were lower at week 4 (6.5, IQR: 3–12, p=0.126) and week 8 (5, IQR: 1.5–56, p=0.066). All five patients whose baseline plasma taurine levels were below the normal limit showed increased taurine levels at week 4; 60% of them experienced improvements in their muscle cramps. Of the five patients with normal or higher taurine levels, 80% experienced an improvement in symptoms at week 4. The safety and tolerability of the 4-week taurine therapy were excellent.

Conclusion: Oral taurine therapy for 4 weeks improved muscle cramps safely in cirrhotic patients.

Key Words: Liver cirrhosis, muscle cramp, taurine
tion deteriorates (i.e., as serum albumin levels decrease or bilirubin levels increase). It has been recently suggested that the mechanism of muscle cramp could include an electrolyte imbalance involving magnesium (Mg) or zinc (Zn) deficiencies, nerve dysfunction due to oxidative stress, and impaired energy metabolism in the skeletal muscle cells.

Several agents have been investigated as therapeutic options for muscle cramps in cirrhotic patients. These included quinine, baclofen, vitamin E, L-carnitine, and branched-chain amino acids. While previous studies have reported favorable responses, most of these studies were small case series. Although several randomized controlled trials have been performed, none have demonstrated a significant improvement in muscle cramp frequency with vitamin E, while some have also reported more frequent adverse events, such as dizziness and diarrhea, for quinidine compared to a placebo.

Taurine has been suggested as a therapeutic agent for muscle cramps due to its stabilizing effect on the skeletal muscle cell membrane. Though several studies have investigated its effect on muscle cramps in patients with chronic liver disease, these studies were small and involved heterogeneous liver disease patients. Furthermore, the dose of taurine administered also differed. No study has investigated the effect of taurine in Korean LC patients with muscle cramps, as taurine is not readily available in South Korea. Therefore, in this study, we investigated whether a drinking formula containing taurine 3 g/day safely improves muscle cramps in Korean LC patients. Additionally, the blood levels of taurine and other electrolytes were measured to analyze their correlations with muscle cramps.

**MATERIALS AND METHODS**

**Subjects**
In this prospective single-arm study, 10 LC patients above 18 years of age who had experienced muscle cramps one or more times per week in the recent 3 months were consecutively enrolled in a tertiary hospital from March to October 2017. LC was diagnosed if the patients presented with at least two of the following: 1) thrombocytopenia (<120000/mm³), 2) ascites, 3) esophageal or gastric varices, 4) nodular appearance during abdominal ultrasound or computed tomography, and 5) pathologically proven cirrhosis. Patients were excluded if they were pregnant or lactating or if they presented with chronic kidney disease, creatinine clearance <30 mL/min/1.73 m², uncontrolled hepatic encephalopathy, or pre-existing neuromuscular diseases, including motor neuron diseases or peripheral neuropathy. All participants provided informed consent voluntarily, and the study was conducted in accordance with the guidelines of the Helsinki Declaration. This study was approved by the Institutional Review Board of Seoul National University Bundang Hospital (B-1605/346-006).

**Study drug and design**
All enrolled participants consumed 3 g of taurine per day (1 g, thrice) for 4 weeks. The study drug was a solution of 1 g taurine in 50 mL water (Dona-A ST, Youngin, Korea) that was contained in a bottle. At every visit, all drug bottles prescribed at the last visit were returned, and the number of empty bottles was counted to check compliance strictly. After 4 weeks of active treatment, all subjects were monitored for an additional 4 weeks to determine whether the status of muscle cramps changed after discontinuation of taurine.

A structured questionnaire was used to assess changes in the frequency, intensity, and duration of muscle cramps with respect to aggravating or relieving factors at baseline and at 1, 2, 4, 6, and 8 weeks after treatment initiation (Supplementary Material, only online). A muscle cramp score was calculated by multiplying the weekly frequency and intensity of cramps. Comorbidities and comedications were recorded.

Blood was sampled at baseline and weeks 4 and 8 for determining plasma taurine levels, serum Mg and Zn levels, complete blood count, and liver function. The plasma taurine levels were measured by high-performance liquid chromatography using the Agilent Series 1100 HPLC system, and the ZORBAX Eclipse Plus C18 columns; measurement was performed as per the manufacturer’s instruction (Agilent, Santa Clara, CA, USA).

**Statistical analysis**
All statistical analyses were performed using Stata version 14.0 (StataCorp LP, College Station, TX, USA). Descriptive statistics were used for demographic data. Changes in the frequency and intensity of muscle cramps at weeks 4 and 8 with respect to baseline were assessed using the Wilcoxon signed-rank test or the Friedman test to detect differences across multiple response measurements as a non-parametric analysis. The Mann-Whitney U test was used to compare muscle cramp scores between subgroups categorized according to baseline plasma taurine levels. Associations among plasma taurine, serum Zn or Mg, and muscle cramp scores were estimated by Spearman correlation analysis. A p value of <0.05 was considered statistically significant.

**RESULTS**

**Baseline patient characteristics**
The median age of the enrolled patients was 66 years [interquartile range (IQR): 58–75 years] and 6 patients (60%) were males (Table 1). Ascites were observed in 7 (70%). 6 (60%) patients had taken diuretics. The etiologies of LC included hepatitis B virus infection (n=4), hepatitis C virus infection (n=4), and alcohol (n=2). Regarding comorbidities, three patients had diabetes mellitus and four had hypertension. The median serum sodium, potassium, and calcium levels were within the normal ranges (Table 1); however, the median serum Zn level...
was lower (57 μg/dL) than the normal limit (80–120 μg/dL). The median study drug compliance was 98.5% (range: 90.5–100%, data not shown). One subject experienced mild dyspepsia as an adverse event associated with the study drug.

**Characteristics of muscle cramps in LC patients at baseline**

The median frequency of muscle cramps was 4.5 times/week (IQR: 2–21 times/week) (Table 2). All subjects reported experiencing severe pain (score ≥4 on a pain scale of 5). The most common site of muscle cramping was the calf (100%), followed by the foot (40%), hand (40%), and thigh (20%). 7 patients (70%)...
experienced pain at multiple sites. In all patients, the pain developed at night (100%), and in 50% of the patients, it lasted for 1–5 minutes. Exercise aggravated muscle cramps in 3 patients (30%), 6 patients (60%) developed cramps during sleep. 6 (60%), 2 (20%), and 1 (10%) patients used massage, stretching, and herbal supplements to relieve pain, respectively; however, 2 patients (20%) recovered spontaneously. Muscle cramps limited labored work in 8 patients (80%) (Table 2).

Changes in muscle cramps after taurine supplementation in LC patients
The frequency (Fig. 1A), intensity (Fig. 1B), and scores (frequency × intensity, Fig. 1C) of muscle cramps during and after four weeks of taurine supplementation (3 g/day) are shown in Fig. 1. Improvement in muscle cramps through weeks 4 and 8 was not statistically significant (frequency, \( p = 0.054 \); intensity, \( p = 0.390 \); and frequency × intensity, \( p = 0.068 \)). Compared to baseline, the intensity of muscle cramps significantly decreased at week 4 (\( p = 0.023 \), Fig. 1B). Fig. 1D indicates the individual changes in the muscle cramp scores of each subject. While muscle cramp scores reduced in 7 patients (70%) by week 4, it improved by week 8 in 2 patients (20%) in whom the score did not decrease by week 4 (Cases #4 and #6 in Table 3). Seven patients (70%) showed a durable response after stopping taurine therapy (until week 8), although three patients showed early or late recurrence (Cases #1, #8, and #9 in Table 3).

Associations of plasma taurine and serum magnesium and zinc levels with muscle cramps in LC patients
At baseline, the median plasma taurine level was 73.5 μM/L (IQR: 40.7–401.9 μM/L) and was within the reference range (65–179 μM/L); however, 5 patients (50%) had taurine levels below the reference limit (<65 μM/L). After 4 weeks of taurine supplementation, the median plasma taurine level increased to 111.9 μM/L (IQR: 69.5–476.2 μM/L; \( p = 0.475 \)). After discon-
tinuation of taurine for 4 weeks, the median plasma taurine level at week 8 decreased to 55.5 μM/L (IQR: 33.6–162.2 μM/L); however, this was not significantly different from the levels at week 4 \((p=0.203)\) or at baseline \((p=0.328)\). Nonetheless, all five patients with low baseline plasma taurine levels showed an increased taurine level after 4 weeks of taurine supplementation; among these, 3 (60%) and 4 (80%) patients experienced an improvement in the muscle cramps at weeks 4 and 8, respectively. Among the remaining five patients with normal or higher taurine levels, 4 (80%) and 3 (60%) patients had an improved muscle cramp score at weeks 4 and 8, respectively (Fig. 2).

Muscle cramp scores tended to be lower in patients with low taurine levels (median score: 8, IQR: 6–12) than in patients with normal or higher taurine levels (median score: 70, IQR: 30–84, \(p=0.058\)). This suggested that taurine level is not a major determinant of muscle cramps. As shown in Fig. 3A, plasma taurine levels were not significantly correlated with muscle cramp scores \((p=-0.02, p=0.306)\). After 4 weeks of taurine therapy, plasma taurine levels increased in six patients (60%; Cases #1–5 and #9 in Table 3); among these, four patients experienced an improvement in symptoms at week 4 (Cases #2, #3, #5, and #9), while one patient (16.7%) experienced recurrence after stopping the therapy (Case #9, Table 3) in spite of a remarkably high drug compliance (98.5%).

As electrolytes potentially correlated with muscle cramps, serum Mg and Zn levels were analyzed in relation to muscle cramp scores. Median Mg levels at baseline, week 4, and week 8 were 2.1 (IQR: 1.9–2.1), 1.9 (IQR: 1.9–1.9), and 1.9 (IQR: 1.8–2.1) mg/dL, respectively \((p=0.056)\). The median Zn levels at baseline, week 4, and week 8 were 57 (IQR: 49–63), 60 (IQR: 57–63), and 55 (IQR: 52–59) μg/dL, respectively \((p=0.166)\). Serum Mg levels were positively correlated with muscle cramp score \((p=0.410, p=0.042, \text{Fig. 3B})\), while serum Zn levels were not \((p=0.197, p=0.346, \text{Fig. 3C})\).

**DISCUSSION**

In this study, we noted that daily supplementation of an oral solution of 3 g taurine for 4 weeks improved muscle cramps in 70% and 80% of LC patients by weeks 4 and 8, respectively. Around 50% of the patients exhibited lower taurine levels at baseline, and taurine supplementation in these individuals tended to provide a durable benefit. During the 4-week taurine therapy, no serious adverse events were observed.

Matsuzaki et al.\(^2\) reported that muscle cramps disappeared with taurine supplementation (3 g thrice daily for 5–24 months, \(n=11\)) in 72.7% of their patients and with taurine supplementation (6 g thrice daily for 6 months, \(n=12\)) in 67% of cirrhotic patients. Yamamoto\(^2\) indicated that a lower dose of taurine (3 g/day for 4 weeks, \(n=35\)) resulted in the disappearance and improvement of muscle cramps in 37.1% and 71.4% of the patients, respectively, which is similar to the present study. However, these studies were published as letters; therefore, the methods for assessing compliance to taurine replacement and measuring muscle cramps in the study populations were unclear. According to a meta-analysis\(^2\) on 77 patients (from five prospective treatment reports and one case study), the use of 3–18 g of taurine daily for 4–24 weeks resolved or improved muscle cramps in all subjects. Moreover, serious adverse events were not reported. Furthermore, a recent placebo-controlled, cross-over designed trial\(^2\) in Australian patients using taurine capsules (1 g/day for 2 weeks and 2 g/day for the subsequent 2 weeks) showed that 2 g/day of taurine significantly reduced the frequency, duration, and severity of muscle cramps. In that study, the subjects’ mean age was 54 years, and 61.2% (30/49) had completed the study protocol taking taurine. Compared to these previous studies, our study clearly demonstrated high adherence to an oral taurine solution (98.5% of compliance), which improved muscle cramps in 70% of the subjects.

The serial measurement of blood taurine, Mg, and Zn levels in the study population was a strength of this study. At base-

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**Table 3. Changes in Plasma Taurine Levels and Muscle Cramp Scores in Korean Liver Cirrhosis Patients at Baseline and at 4 and 8 Weeks after Initiation of Taurine Supplementation**

| No | Age | Sex | Plasma taurine level (μM/L)* | Muscle cramp score (frequency × intensity) | Muscle cramp frequency (times/week) |
|----|-----|-----|-----------------------------|------------------------------------------|-----------------------------------|
|    |     |     | Baseline | Week 4 | Week 8 | Baseline | Week 4 | Week 8 | Baseline | Week 4 | Week 8 |
| 1  | 75  | F   | 18.4     | 4      | 10     | 6      | 1      | 2      | 1.5     |
| 2  | 43  | M   | 36.0     | 12     | 4      | 2      | 3      | 1      | 0.5     |
| 3  | 58  | M   | 40.8     | 105    | 2      | 0      | 21     | 0.5    | 0       |
| 4  | 72  | M   | 53.5     | 8      | 28     | 4      | 2      | 14     | 2       |
| 5  | 62  | M   | 55.9     | 6      | 3      | 1      | 2      | 1      | 0.5     |
| 6  | 80  | F   | 90.3     | 105    | 112    | 56     | 21     | 28     | 14      |
| 7  | 62  | M   | 135.8    | 30     | 6      | 6      | 6      | 2      | 2       |
| 8  | 79  | M   | 401.9    | 84     | 12     | 84     | 21     | 6      | 21      |
| 9  | 52  | F   | 629.6    | 70     | 7      | 84     | 14     | 7      | 28      |
| 10 | 70  | F   | 660.0    | 8      | 2      | 1.5    | 2      | 1      | 0.5     |

*Reference level: 65–179 μM/L, †Improvement from baseline.
line, the plasma taurine level was below normal in five of the 10 cirrhotic patients in this study. A 4-week taurine replacement achieved normal plasma taurine levels in all patients by week 4; however, neither the plasma taurine level nor its increase were individually correlated with muscle cramp scores. Notably, two patients (Cases #8 and #9 in Table 3) who showed rebound aggravation of muscle cramps after taurine supplementation had very high plasma taurine levels at baseline, which may have attenuated the effect of oral taurine supplementation. Taurine concentrations can change in stress states, such as osmotic changes or anoxia, and with the intake of taurine-rich foods, such as seafood, fish, meat, and dairy. A randomized controlled study reported that in response to oral taurine replacement with a titrated dose of 1–2 g/day for 4 weeks,
the mean serum taurine level in the taurine-treated group increased by 2.5 times (178±19 μmol/L) from baseline (59±3 μmol/L), while that in the placebo group (67±6 μmol/L) remained similar to baseline (reference range: 50–100 μmol/L).

However, correlation between muscle cramps and serum taurine level was not investigated in that study. The present study showed that subjects with very low baseline taurine levels benefitted from taurine supplementation, as most of these patients experienced an improvement in muscle cramps after taurine therapy.

Recently, two hypotheses have been suggested for the mechanism of muscle cramp development. The first is the electrolyte depletion/dehydration hypothesis that focuses on the shift in interstitial fluid due to electrolyte deficiency, which results in the alteration of nerve excitability. The second is the neuromuscular hypothesis that emphasizes muscle fatigue resulting from an imbalance between excitation from the muscle spindle and inhibition from the Golgi system. Theoretically, taurine replacement is expected to enhance neuromuscular stability in cirrhotic patients, consequently improving muscle cramps therein; however, there are various factors that affect both electrolyte balance and muscle cell stability. Because plasma taurine and serum Mg and Zn deficiencies were not significantly related with muscle cramp scores in the present study, the mechanism of symptom improvement with taurine supplementation remains unclear. This study had a limitation as a single-arm pilot study and enrolled a limited number of subjects.

Nonetheless, our results stress the need for assessment of and interventions for muscle cramps in cirrhotic patients. Further studies considering various determinants of neuronal activity and the effect of hepatic impairment on them are warranted to understand the entire mechanism of muscle cramps in cirrhotic patients.

In conclusion, muscle cramps are a significantly problematic symptom that lowers quality of life in cirrhotic patients. These patients could benefit from an attempt to address and control the symptoms. A 4-week oral taurine solution therapy showed excellent compliance and safety, with improvement in muscle cramps in most study subjects, regardless of an increase in blood taurine. The mechanism of the symptom improvement needs to be elucidated in a larger-scale study.

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AUTHOR CONTRIBUTIONS

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