Original Article
Yonsei Med J 2021 Jan;62(1):21-28
https://doi.org/10.3349/ymj.2021.62.1.21
Yonsei Medical Journal
YMJ
pISSN: 0513-5796 · eISSN: 1976-2437

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

Eun Sun Jang[1], Sung Ho Hwang[2], Jin-Wook Kim[1], and Sook-Hyang Jeong[1]

[1]Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam; [2]Department of Nursing, Suwon Science College, Hwaseong, Korea.

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

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-

Received: September 22, 2020 **Revised:** October 28, 2020
Accepted: November 24, 2020
Corresponding author: Sook-Hyang Jeong, MD, Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Bundang Hospital, 82 Gumi-ro 173 beon-gil, Bunddang-gu, Seongnam 13620, Korea. Tel: 82-31-787-7034, Fax: 82-31-787-4052, E-mail: jsh@snubh.org

•The authors have no potential conflicts of interest to disclose.

tion deteriorates (i.e., as serum albumin levels decrease or bilirubin levels increase).[4,5] 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.[9]

Several agents have been investigated as therapeutic options for muscle cramps in cirrhotic patients. These included quinine,[10] baclofen,[11,12] Zn,[13] vitamin E,[14,15] L-carnitine,[16,17] and branched-chain amino acids.[18,19] 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,[15] while some have also reported more frequent adverse events, such as dizziness and diarrhea, for quinidine,[20] 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.[21] 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/mm^3), 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 m^2, 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[8] 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

https://doi.org/10.3349/ymj.2021.62.1.21

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.

Table 1. Baseline Characteristics of Enrolled Patients

Variables	n=10
Age, yr	66 (58–75)
Sex	
Male/female	6 (60)/4 (40)
Body mass index, kg/m^2	25.7 (23.9–26.8)
Alcohol	
Never/quit	6 (60)/4 (40)
Child-Pugh class	
A/B	2 (20)/8 (80)
MELD score	12.5 (10–14)
Ascites, yes	7 (70)
Comorbidities	4 (40)
Diabetes	3 (30)
Hypertension	4 (40)
Comedications	
Diuretics	6 (60)
Anti-hypertensive	4 (40)
Oral hypoglycemic agents	3 (30)
Propranolol	3 (30)
Pregabalin	1 (10)
Branched-chain amino acid	4 (40)
Laboratory findings	
WBC, /mm^3	3870 (2710–4970)
Hb, g/dL	12.7 (11.7–13.4)
PLT, ×1000/mm^3	79 (63–91)
Cholesterol, mg/dL	125.5 (119–147)
Bilirubin, mg/dL	1.85 (1.1–2.3)
Albumin, g/dL	3.2 (3.1–3.4)
AST, IU/L	57 (42–65)
ALT, IU/L	37 (25–43)
GGT, IU/L	38 (29–63)
PT (INR)	1.31 (1.24–1.35)
BUN, mg/dL	16.5 (14–19)
Cr, mg/dL	0.84 (0.77–1.23)
Fasting glucose, mg/dL	109 (97–122)
Na, mM/L	137.5 (134–140)
K, mM/L	4.3 (3.8–4.6)
Ca, mg/dL	8.7 (8.3–8.9)
Zn, ug/dL*	57 (49.5–61)
Mg, mg/dL*	2 (1.95–2.1)
Taurine, μM/L*	73.5 (40.7–401.9)

MELD, Model For End-Stage Liver Disease; WBC, white blood cell; Hb, hemoglobin; PLT, platelet; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma glutamyl-transferase; PT, prothrombin time; INR, international normalized ratio; BUN, blood urea nitrogen; Cr, creatinine; Na, sodium; K, potassium; Ca, calcium; Zn, zinc; Mg, magnesium.
Median (interquartile range) or number (%).
*Reference levels: taurine, 65–179 μM/L; Zn, 66–110 ug/dL; Mg, 1.5–2.5 mg/dL.

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%)

Table 2. Baseline Characteristics of Muscle Cramps in Liver Cirrhosis Patients

Characteristics of muscle cramps	No (%)
Frequency	
≥7 times/week	4 (40)
1–6 times/week	6 (60)
Intensity	
Severe	10 (100)
Mild	0 (0)
Site	
Calf	10 (100)
Thigh	2 (20)
Foot	4 (40)
Hand	4 (40)
No. of painful sites	
1	3 (30)
2	5 (50)
≥3	2 (20)
Time	
Day	0 (0)
Night	7 (70)
Both	3 (30)
Duration (min)	
<1	1 (10)
1– 5	5 (50)
5–10	2 (20)
10–30	2 (20)
Aggravating factor	
Exercise	3 (30)
Post-exercise	1 (10)
Cold	2 (20)
Rest	5 (50)
Sleeping	6 (60)
Relieving factor	
Spontaneously	2 (20)
Herbal supplements	1 (10)
Massage	6 (60)
Stretching	2 (20)
Difficulties in life	
Often limited daily life	2 (20)
Limited labored work	3 (30)
Often limited labored work	5 (50)

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);[22] 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-

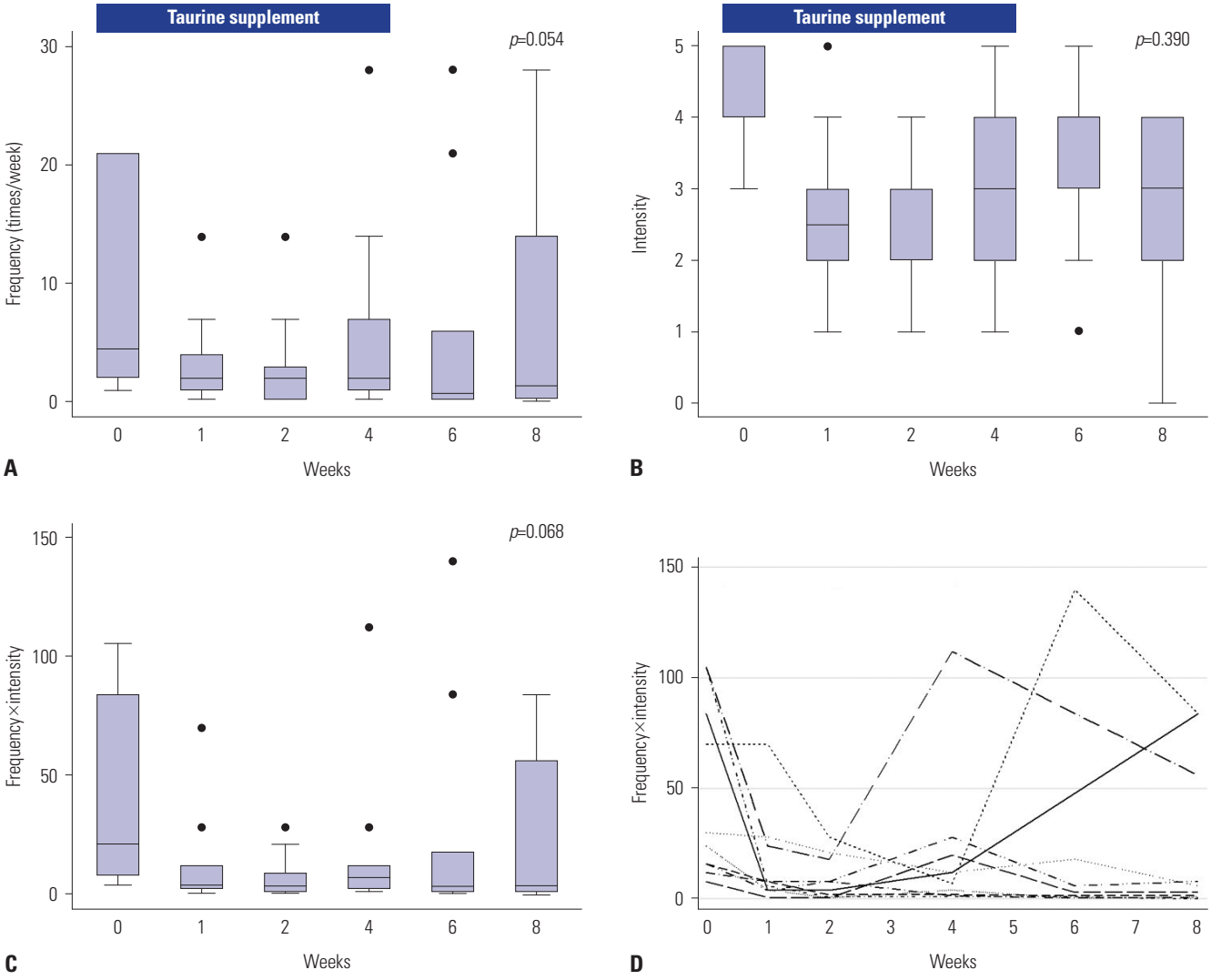

Fig. 1. Changes in the frequency of muscle cramps (A), intensity of muscle cramps (B), and muscle cramp scores (C, overall; D, individually) in Korean liver cirrhosis patients before and after taurine replacement.

https://doi.org/10.3349/ymj.2021.62.1.21

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 (ρ=-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 (ρ=0.410, p=0.042, Fig. 3B), while serum Zn levels were not (ρ=-0.197, p=0.346, 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.[23,24] 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[21] 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[25] 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[26] 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-

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	147.8†	329.2	4	10	6	1	2	1.5
2	43	M	36.0	75.9†	25.6	12	4†	2†	3	1†	0.5†
3	58	M	40.8	67.9†	43.1	105	2†	0†	21	0.5†	0†
4	72	M	53.5	476.2†	33.6	8	28	4†	2	14	2†
5	62	M	55.9	71.1†	162.2	6	3†	1†	2	1†	0.5†
6	80	F	90.3	63.1	151.8	105	112	56†	21	28	14†
7	62	M	135.8	69.5	43.1	30	6†	6†	6	2†	2†
8	79	M	401.9	346.8	67.9	84	12†	84	21	6†	21
9	52	F	629.6	976.4†	205.4	70	7†	84	14	7†	28
10	70	F	660.0	539.4	4.0	8	2†	1.5†	2	1†	0.5†

*Reference level: 65–179 μM/L, †Improvement from baseline.

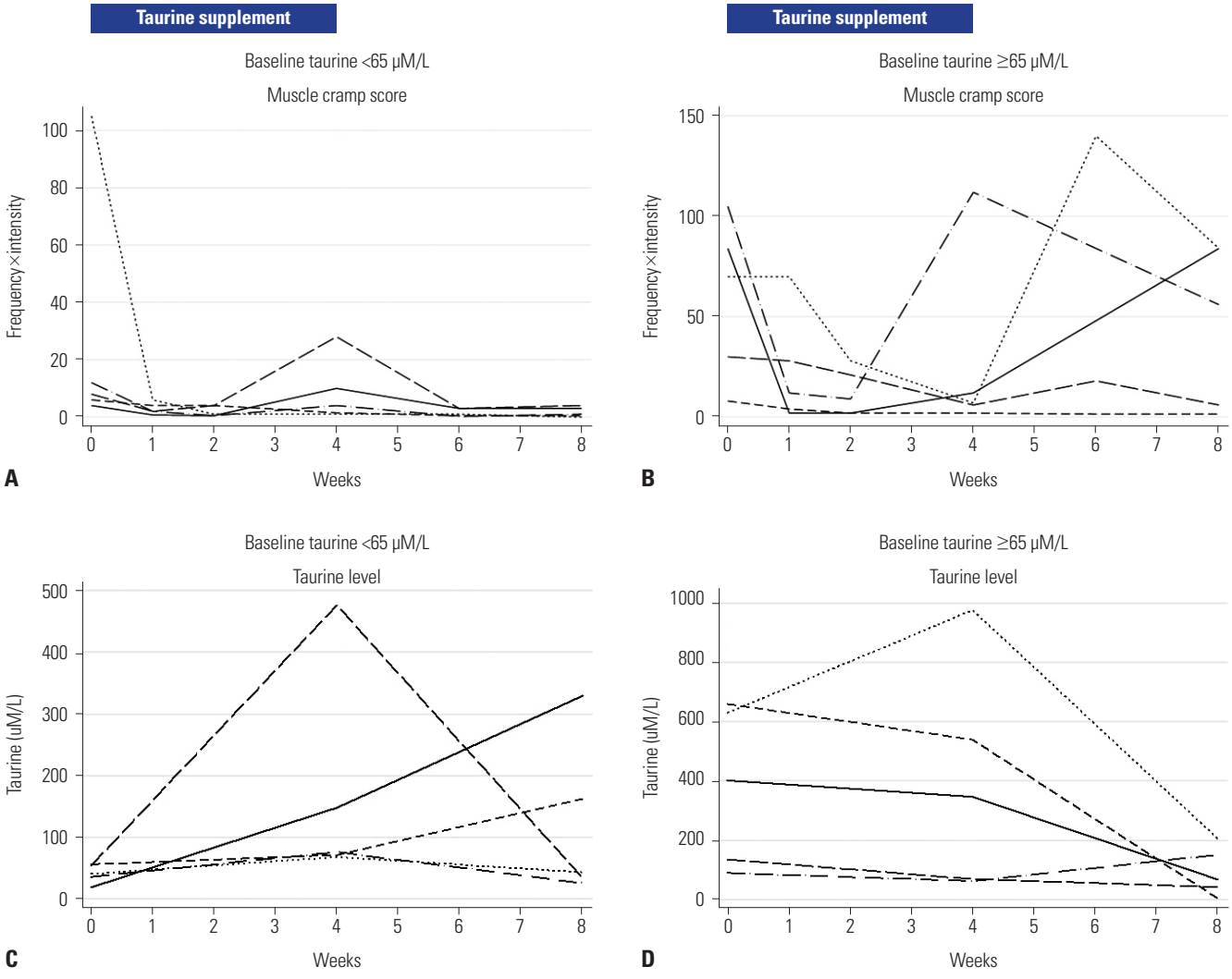

Fig. 2. Change in muscle cramp scores (A and B) and plasma taurine levels (C and D) according to baseline taurine levels in Korean liver cirrhosis patients before and after taurine replacement.

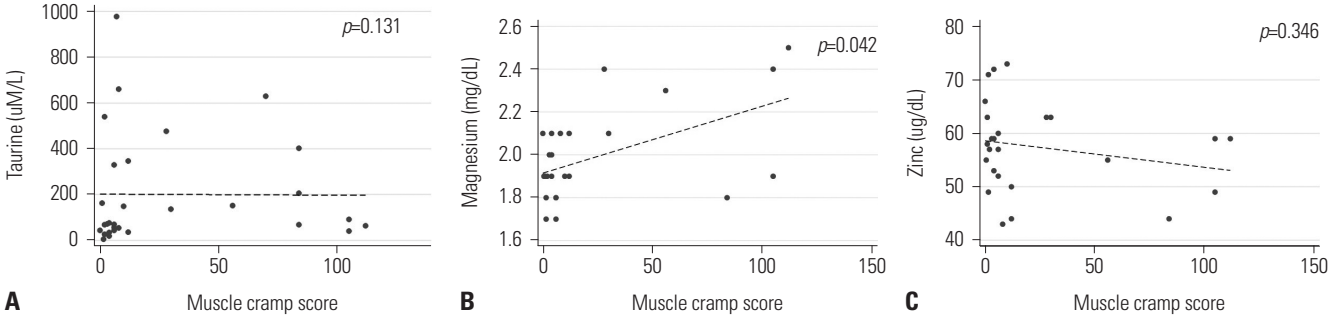

Fig. 3. Associations among plasma taurine (A), serum magnesium (B), and serum zinc (C) levels, and muscle cramp scores in liver cirrhosis patients.

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,[27] and with the intake of taurine-rich foods, such as seafood, fish, meat, and dairy.[28] A randomized controlled study[26] reported that in response to oral taurine replacement with a titrated dose of 1–2 g/day for 4 weeks,

https://doi.org/10.3349/ymj.2021.62.1.21

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.[29] 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 s 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.

ACKNOWLEDGEMENTS

This study was funded by Dong-A Pharmaceutical.
The authors are grateful to the devoted research coordinator Dawoon Jeong.

AUTHOR CONTRIBUTIONS

Conceptualization: Eun Sun Jang and Sook-Hyang Jeong. Data curation: all authors. Formal analysis: Eun Sun Jang. Funding acquisition: Sook-Hyang Jeong. Investigation: all authors. Methodology: all authors. Project administration: Sook-Hyang Jeong. Resources: all authors. Software: Eun Sun Jang. Supervision: Sook-Hyang Jeong. Validation: all authors. Visualization: Eun Sun Jang. Writing—original draft: Eun Sun Jang. Writing—review & editing: all authors. Approval of final manuscript: all authors.

ORCID iDs

Eun Sun Jang https://orcid.org/0000-0003-4274-2582
Sung Ho Hwang https://orcid.org/0000-0001-5356-1993
Jin-Wook Kim https://orcid.org/0000-0003-0934-3344
Sook-Hyang Jeong https://orcid.org/0000-0002-4916-7990

REFERENCES

1. Miller TM, Layzer RB. Muscle cramps. Muscle Nerve 2005;32:431-42.
2. Chatrath H, Liangpunsakul S, Ghabril M, Otte J, Chalasani N, Vuppalanchi R. Prevalence and morbidity associated with muscle cramps in patients with cirrhosis. Am J Med 2012;125:1019-25.
3. Murata A, Hyogo H, Nonaka M, Sumioka A, Suehiro Y, Furudoi A, et al. Overlooked muscle cramps in patients with chronic liver disease: in relation to the prevalence of muscle cramps. Eur J Gastroenterol Hepatol 2019;31:375-81.
4. Konikoff F, Theodor E. Painful muscle cramps. A symptom of liver cirrhosis? J Clin Gastroenterol 1986;8:669-72.
5. Abrams GA, Concato J, Fallon MB. Muscle cramps in patients with cirrhosis. Am J Gastroenterol 1996;91:1363-6.
6. Marotta PJ, Graziadei IW, Ghent CN. Muscle cramps: a 'complication' of cirrhosis. Can J Gastroenterol 2000;14 Suppl D:21D-5D.
7. Marchesini G, Bianchi G, Amodio P, Salerno F, Merli M, Panella C, et al. Factors associated with poor health-related quality of life of patients with cirrhosis. Gastroenterology 2001;120:170-8.
8. Iwasa M, Karino Y, Kawaguchi T, Nakanishi H, Miyaaki H, Shiraki M, et al. Relationship of muscle cramps to quality of life and sleep disturbance in patients with chronic liver diseases: a nationwide study. Liver Int 2018;38:2309-16.
9. Mehta SS, Fallon MB. Muscle cramps in cirrhosis: a moving target. Clin Gastroenterol Hepatol 2015;13:1544-6.
10. Corbani A, Manousou P, Calvaruso V, Xirouchakis I, Burroughs AK. Muscle cramps in cirrhosis: the therapeutic value of quinine. Is it underused? Dig Liver Dis 2008;40:794-9.
11. Elfert AA, Abo Ali L, Soliman S, Zakaria S, Shehab El-Din I, Elkhalawany W, et al. Randomized placebo-controlled study of baclofen in the treatment of muscle cramps in patients with liver cirrhosis. Eur J Gastroenterol Hepatol 2016;28:1280-4.
12. Henry ZH, Northup PG. Baclofen for the treatment of muscle cramps in patients with cirrhosis: a new alternative. Hepatology 2016;64:695-6.
13. Kugelmas M. Preliminary observation: oral zinc sulfate replacement is effective in treating muscle cramps in cirrhotic patients. J Am Coll Nutr 2000;19:13-5.
14. Konikoff F. The therapeutic benefit of vitamin E in patients with liver disease. J Hepatol 1994;21:687-8.
15. Chandok N, Tan P, Uhanova J, Shankar N, Marotta P. A pilot study of vitamin E for the treatment of cirrhotic muscle cramps. Liver Int 2011;31:586-7.
16. Nakanishi H, Kurosaki M, Tsuchiya K, Nakakuki N, Takada H, Matsuda S, et al. L-carnitine reduces muscle cramps in patients with cirrhosis. Clin Gastroenterol Hepatol 2015;13:1540-3.
17. Imbe A, Tanimoto K, Inaba Y, Sakai S, Shishikura K, Imbe H, et al. Effects of L-carnitine supplementation on the quality of life in diabetic patients with muscle cramps. Endocr J 2018;65:521-6.

18. Sako K, Imamura Y, Nishimata H, Tahara K, Kubozono O, Tsubouchi H. Branched-chain amino acids supplements in the late evening decrease the frequency of muscle cramps with advanced hepatic cirrhosis. Hepatol Res 2003;26:327-9.
19. Hidaka H, Nakazawa T, Kutsukake S, Yamazaki Y, Aoki I, Nakano S, et al. The efficacy of nocturnal administration of branched-chain amino acid granules to improve quality of life in patients with cirrhosis. J Gastroenterol 2013;48:269-76.
20. Lee FY, Lee SD, Tsai YT, Lai KH, Chao Y, Lin HC, et al. A randomized controlled trial of quinidine in the treatment of cirrhotic patients with muscle cramps. J Hepatol 1991;12:236-40.
21. Yamamoto S. Oral taurine therapy for painful muscle cramp in liver cirrhosis. Am J Gastroenterol 1994;89:457-8.
22. Ghandforoush-Sattari M, Mashayekhi S, Nemati M, Routledge PA. A rapid determination of taurine in human plasma by LC. Chromatographia 2009;69:1427-30.
23. Matsuzaki Y, Tanaka N, Yamaguchi T, Chuganji Y, Nishi M, Chiba T, et al. Effect of taurine administration for muscle cramp in chronic liver disease: a case of decompensated liver cirrhosis in which muscle cramp disappeared after oral administration of taurine. Kanzo 1990;31:1464-9.
24. Matsuzaki Y, Tanaka N, Osuga T. Is taurine effective for treatment of painful muscle cramps in liver cirrhosis? Am J Gastroenterol 1993;88:1466-7.
25. Vidot H, Carey S, Allman-Farinelli M, Shackel N. Systematic review: the treatment of muscle cramps in patients with cirrhosis. Aliment Pharmacol Ther 2014;40:221-32.
26. Vidot H, Cvejic E, Carey S, Strasser SI, McCaughan GW, Allman-Farinelli M, et al. Randomised clinical trial: oral taurine supplementation versus placebo reduces muscle cramps in patients with chronic liver disease. Aliment Pharmacol Ther 2018;48:704-12.
27. Ghandforoush-Sattari M, Mashayekhi S, Krishna CV, Thompson JP, Routledge PA. Pharmacokinetics of oral taurine in healthy volunteers. J Amino Acids 2010;2010:346237.
28. Purchas RW, Rutherfurd SM, Pearce PD, Vather R, Wilkinson BH. Concentrations in beef and lamb of taurine, carnosine, coenzyme Q(10), and creatine. Meat Sci 2004;66:629-37.
29. Giuriato G, Pedrinolla A, Schena F, Venturelli M. Muscle cramps: a comparison of the two-leading hypothesis. J Electromyogr Kinesiol 2018;41:89-95.

https://doi.org/10.3349/ymj.2021.62.1.21