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Original Research

Effect of ursodeoxycholic acid on chronic liver diseases and S.G.O.T/S.G.P.T level

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ABSTRACT:

Aim: The aim of this study was to assess the effects of ursodeoxycholic acid composite (URSA-S) on fatigue in patients with elevated liver function tests and/or fatty liver disease. **Methods:** In this randomised double-blinded placebo- controlled trial, 20 adults who were diagnosed with fatigue based on our criteria and had elevated liver function tests (but not > 5 times the normal level) and/or fatty liver on ultrasonography, were randomised to either the placebo or URSA-S administration group. The rate of improvement of checklist individual strength (CIS) using a cut-off of 76 points at the end of the study (8 weeks), the change in fatigue scale [CIS score and visual analogue scale (VAS)] were evaluated. The adverse effects of URSA-S were also recorded. **Results:** The rate of CIS improvement at the end-point was 79.76% and 45.68% in the therapy and placebo groups, respectively ($p < 0.05$). The difference in fatigue recovery rate between the therapy and placebo groups was significant after 8 weeks. When analysed separately in patients with abnormal liver function tests and fatty liver disease, the fatigue recovery rate of the CIS score and VAS at 8 weeks was higher in the therapy than in the placebo group ($p < 0.05$). The frequency of adverse events in the therapy group was not significantly higher than that in the placebo group. **Conclusion:** URSA-S is effective for alleviating fatigue in patients with liver dysfunction and/or fatty liver. The adverse effects of URSA-S are not significant.

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INTRODUCTION

Ursodeoxycholic acid (ursodiol) may be beneficial in patients with intrahepatic cholestasis or chronic liver disease because of its cytoprotective or choleretic action. This has been demonstrated from both clinical and experimental investigation [(I-3).]

URSA-S comprises 50 mg of ursodeoxycholic acid (UDCA), 10 mg of thiamine nitrate, and 5 mg of riboflavin. It is used for the treatment of cholestatic liver diseases, gallstone and fatty liver, as well as among patients with hepatitis virus infection to ameliorate the elevated alanine aminotransferase levels in East Asia [(4–6)]. URSA-S is also beneficial for liver regeneration in cases of non-alcoholic fatty liver disease (NAFLD) [(7)]. The suggested mechanisms of URSA-S include the improvement of bile acid transport and/or detoxification, cytoprotection and anti-apoptotic effects [(8–10)]. URSA-S activates AMP-activated protein kinase (AMPK) in the liver, which suggests that URSA-S may serve as an AMPK agonist [(11)]. It is also known to play a major role in energy homoeostasis. These findings suggest that URSA-S has a beneficial effect on the regulation of energy production.

We have noted similar results from our nonrandomized, open-label study of the effects of ursodiol in chronic active and inactive hepatitis as well as in primary biliary cirrhosis. In this article we present preliminary findings from this study.

MATERIALS AND METHODS

Among the male and female individuals aged ≥ 19 years who visited one of the five general hospitals, we enrolled patients who presented with persistent fatigue for > 1 month and at least one abnormal liver function parameter within the last 4 weeks or fatty liver, from

October 2014 to March 2015. The presence of fatty liver within the last 3 months was proved by using the medical records. Patients were considered to be eligible for study enrolment if they met all the following inclusion criteria: (i) > 19 years of age; (ii) persistent or chronic fatigue for ≥ 1 month upon screening; (iii) total CIS score of ≥ 76 points upon screening and at baseline; (iv) Hospital Anxiety and Depression Scale (HADS) score of ≤ 10 points upon screening; (v) abnormal serum ALT levels within the last 4 weeks or presence of fatty liver on ultrasonography within the last 3 months and (vi) voluntary agreement to participate in the clinical trials and provision of informed consent.

Patients were excluded from the study if they met one of the following conditions: (i) liver cirrhosis, liver cancer, severe hepatic dysfunction (five times more than the normal upper limit of serum ALT level), renal dysfunction (two times more than the normal upper limit of serum creatinine) and chronic fatigue syndrome; (ii) known underlying cause of fatigue (such as malignant tumour, active pulmonary tuberculosis, asthma, glaucoma, multiple sclerosis, hypothyroidism, HIV positive status, anaemia, chronic inflammatory diseases such as rheumatoid arthritis etc.); (iii) psychiatric diseases (major depressive disorder, bipolar disorder, schizophrenia, delusional disorder, dementia, etc.); (iv) uncontrolled hypertension (≥ 170/110 mmHg), uncontrolled diabetes (HbA1c ≥ 8.0%) and obesity (BMI ≥ 30); (v) taking medicines or supplements related to fatigue for more than 4 days in 2 weeks (such as beta blockers, glucocorticoids, immune modulators, antidepressants, anxiolytics, sedatives, antipsychotics, vitamins, ginseng, non-steroidal anti-inflammatory drug (NSAID), hormones, traditional oriental medicinal management and materials that can alter liver function as determined by the physicians participating in this study); (vi) pregnant women, breast feeding women, women with an expected delivery date during of within 2 months after the study; (vii) history of alcohol or drug abuse; (viii) individuals who participated in other clinical trials within 1 month of this study; and (ix) other conditions that may make participation in this study inappropriate.

The protocol was approved by the ethical committee of each institution participating in the study. IRB number of the main hospital is IB-1409-040. Patients were informed about the details of the clinical study and voluntarily agreed to participate in the study. We conducted this clinical study in accordance with the Declaration of Helsinki and good clinical practice guidelines.

STUDY DESIGN

This clinical trial was planned as a multi-centre, randomised, double-blinded, placebo-controlled study to evaluate the effect of URSA-S on fatigue in patients with abnormal liver function and/or fatty liver disease.

The eligible participants were assigned to one of two groups with equal probability according to a randomisation code.

After the patients provided informed consent, their medical history and records, laboratory test results, and CIS, VAS and HADS scores were reviewed. The subjects were randomised to the treatment or placebo group, and took either URSA-S or placebo three times daily for 8 weeks.

Checklist individual strength scores; VAS scores; vital signs including blood pressure and pulse pressure; and laboratory examination data were assessed at baseline and 4 and 8 weeks after the start of the study. Adverse events, along with their severity and perceived relation to the study medication, were recorded throughout the study. Serious adverse events (for example, those requiring admission to hospital or that resulted in a persistent or significant disability or incapacity) were also recorded.

The primary efficacy variable of this study was the rate of improvement in CIS scores at the end-point (8 weeks). Improvement was considered a change in the CIS score to ≤ 76. The secondary efficacy variables included changes in the fatigue scale scores (CIS score and VAS).

MEASUREMENT

During screening, the demographic information (age, gender, smoking, drinking and other information), medical history, and medication history of the subjects were investigated and recorded. When clinically significant test results were observed, the investigator decided whether to enrol the subject in the experiment.

The laboratory tests were conducted at baseline, week 4, and week 8. The assessments included complete blood count, liver function test, renal function test, lipid profile and urinalysis conducted at each institute. Haemoglobin A1c level assessment and human immunodeficiency virus test were only performed at the initial visit.

Fatigue alleviation was the primary outcome and was evaluated using self-administered measures of fatigue, including the CIS and VAS scores. The CIS questionnaire consists of four subscales: fatigue severity (CIS-fatigue, eight items), concentration (five items), motivation (four items) and activity level (three items), each of which is scored on a 7-point Likert-scale. Higher total scores represent a higher degree of fatigue. The CIS covers several aspects of fatigue, such as severity, motivation, concentration, and physical activity level, which adhere to the concept of prolonged fatigue. The total CIS cut-off point of 76 was determined, with a specificity of 90% and a sensitivity of 73% (12). The CIS total cut-off point is defined as a score indicating a fatigue level that places the individual ‘at risk’ for sick leave or work disability, and appears to be appropriate for use in studies on fatigue in the working population. The VAS is used to assess the impact of fatigue on daily

life, and the answers range from 'no influence at all' to 'a lot of influence' along a line of 100 mm (range 0–100).

RESULTS

DEMOGRAPHIC DATA AND CHARACTERISTICS OF THE SUBJECTS PRIOR TO TREATMENT

The conditions of the subjects before medication was provided were compared between the groups (Table 1). The mean ages were 43.63 years (SD = 11.79) in the therapy group and 43.72 years (SD = 10.36) in the placebo group. The number of male and female subjects were 20 in the therapy group and 20 in the placebo group. The mean BMI was 26.12 kg/m2 (SD = 2.56) in the therapy group and 26.27 kg/m2 (SD = 2.37) in the placebo group. Moreover, smoking (p = 0.7820), alcohol consumption (p = 0.5616) and caffeine consumption (p = 0.7466) were not significantly different between the two groups. The mean values of HADS score were 12.25 (SD = 4.58) in the therapy group and 11.86 (SD = 4.94) in the placebo group (p = 0.7161). The mean values of the CIS scores were 89.81 and 91.75 in the therapy and placebo groups, respectively. With regard to the other variables, no significant differences in the laboratory test results were observed between the two groups.

Table 1: **Baseline characteristics of the subjects in the full analysis set**

	URSA-S (n = 20)	Placebo (n =20)
Sex		
Men	15	10
Women	5	10
BMI (kg/m2)	26.12 ±2.56	26.27 ±2.37
Smoking		
Non	9	8
Ex	7	7
Current	3	5
Alcohol consumption		
No	12	15
Yes	8	5
Caffeine consumption		
No	3	5
Yes	17	15
HADS score		
Anxiety	5.58 ± 2.80	5.46 ± 2.80
Depression	6.67 ± 2.45	6.41 ± 2.70
Total	12.25 ± 4.58	11.86 ± 4.94
CIS score		
Liver function test	47.58 _ 34.64	48.90 _ 27.08
ALT (SGPT)	32.33 _ 16.27	32.47 _ 11.72
AST (SGOT)	51.33 _ 40.74	58.54 _ 50.22
c-GTP	4.59 _ 0.27	4.61 _ 0.22
Albumin	0.89 _ 0.44	0.82 _ 0.25
T-bilirubin		

CHANGE IN BLOOD CHEMISTRY DATA DURING THE STUDY

No difference in the change in AST or gamma glutamyl transpeptidase (r-GTP) and total bilirubin levels was observed between the therapy and placebo groups at 4 and 8 weeks; however, the change in ALT levels was significant (p = 0.0228) between the therapy group and placebo group at 4 weeks, but not at 8 weeks after the start of the study (p = 0.1278). The mean decreases in the serum ALT levels from the baseline value to after 4 weeks and 8 weeks were 7.45 and 8.31 IU/l, respectively, in the therapy group. The mean decreases in the serum AST levels from the baseline value to after 4 and 8 weeks were 2.74 and 2.81 IU/l, respectively, in the therapy group.

DISCUSSION

We observed that the fatigue recovery rate was higher in the URSA-S therapy group than in the placebo group. This finding was observed independently in patients with abnormal liver function and fatty liver disease.

The term NAFLD describes a condition characterized by excess fat within the liver that affects individuals with minimal or no alcohol consumption. This condition may range from simple fatty liver (steatosis), through fat with necroinflammation and/ or fibrosis – so-called non-alcoholic steatohepatitis (NASH) – to advanced fibrosis, cirrhosis and hepatocellular cancer [(12)]. NAFLD is strongly associated with visceral obesity, insulin resistance, hypertension and dyslipidemia, and is considered to represent the manifestation of metabolic syndrome in

the liver [13]. Given the increase in the incidence of obesity and diabetes in Western countries, NAFLD has become a growing problem, and is currently recognized as the most common liver disease in these countries and the most common cause of incidental abnormal liver blood test results [14].

Fatigue is one of the most common symptoms in patients with liver disease, but it is easily overlooked or underestimated during treatment because it is hard to define and treat. However, worsening of fatigue may lead to increased inactivity or impairment of activities of daily living, which could ultimately lead to a lower quality of life. Hence, it requires appropriate treatment.

Dried black bear's bile, which is rich in ursodeoxycholic acid (URSA-S), is recommended in China for the treatment of jaundice during the period of the Tang dynasty (618–907 AD), as documented in Tang MateriaMedica – the first state pharmacopoeia worldwide. URSA-S was thereafter proposed as a potential therapeutic option for chronic cholestatic disorders with the following rationale: (1) the accumulation of toxic bile acids may be at least in part responsible for liver injury in chronic cholestasis; and (2) the replacement of endogenous bile acids by a non-toxic bile acid (URSA-S) could protect the liver and delay the progression of these disorders.

This hypothesis was first tested in primary biliary cirrhosis [15]. URSA-S was shown to yield marked improvement in serum liver tests [15,16]. Placebocontrolled trials showed that URSA-S also improves the histological features and delays the progression to cirrhosis and the time to liver transplantation [17,18]. At present, URSA-S therapy is recommended for all patients with primary biliary cirrhosis, provided that they exhibit abnormal serum liver test results [19].

The mechanism underlying the anti-fatigue action of URSA-S is not known, but 50-AMP-activated protein kinase (AMPK) activation may be involved.

URSA-S strongly increases AMPK phosphorylation, and AMPK is a key regulator of cellular and wholebody energy balance [20]. AMPK phosphorylates and regulates many proteins involved in nutrient metabolism, by largely acting to suppress anabolic ATP-consuming pathways while stimulating catabolic ATP-generating pathways [21]. These observations suggest that URSA-S has a beneficial effect on the regulation of energy production. The other proposed mechanism is that URSA-S decreases hepatocyte sensitivity to hydrophobic bile acid-induced oxidative stress [22]. Some studies found a significant association between lipid oxidation levels and fatigue[23].

The fatigue recovery rate in CIS scores was approximately 46% in the placebo group, which is relatively higher as compared to that in other studies [24]. There are a few possible causes for this observation. The placebo used in this study had a similar taste and smell and shape, and therefore, the high placebo effect may be because of the high expectation that the received drug would be URSA-S. Second, fatigue may originate from multiple causes, and fatigue is difficult to assess objectively (3). Fatigue scales such as CIS are used to study fatigue and may not represent all the aspects of fatigue [25]. We observed that the mean decrease in serum ALT levels from baseline to after 4 weeks was significantly higher in the therapy group than in the placebo group, although a significant difference was not observed between baseline and the 8-week stage. No significant change in serum AST levels was observed. We included patients with fatty liver and/or abnormal liver function test results (which were not over five times of the normal limits) irrespective of the underlying liver diseases.

The underlying liver disease may include alcoholic liver disease or viral hepatitis. Hence, another limitation of the study is the lack of appropriate assessments of the cause of hepatopathy prior inclusion.

CONCLUSION

URSA-S is found to be effective for alleviating fatigue in patients with abnormal liver function and/or fatty liver. However, no significant difference in the adverse effects is observed between patients administered URSA-S and placebo.

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