Gut and Gastroenterology

RESEARCH ARTICLE

Administration of Nalfurafine Hydrochloride in Patients with Hepatocellular Carcinoma and Refractory Pruritus Improved Patient-Reported Outcome

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Abstract

Background: Patients with hepatocellular carcinoma (HCC) frequently suffer from pruritus, which can severely impair their health-related quality of life (HRQOL). Nalfurafine hydrochloride, a selective κ-opioid receptor agonist, was recently approved in Japan for refractory pruritus in patients with chronic liver diseases, but it still remains unclear whether this treatment improves the patient-reported outcome (PRO) in HCC patients with refractory pruritus. Herein, we conducted a study to investigate the efficacy of nalfurafine hydrochloride in terms of PRO.

Methods: We identified 21 chronic liver disease patients with pruritus after screening for pruritus. The participants received 2.5 μg nalfurafine hydrochloride once daily. Generic HRQOL using short form 36 (SF-36) and the visual analog scale (VAS) were also measured at baseline and at end of treatment.

Results: VAS significantly declined during the study period, from 43.7 ± 34.1 to 14.3 ± 23.8 (p = 0.002) at bedtime between baseline and end of treatment, respectively, indicating a significant effect of nalfurafine hydrochloride. In HCC group, the mean VAS at baseline and at end of treatment was 46.8 ± 35.3 and 13.0 ± 19.4, respectively, representing a more pronounced reduction (p = 0.009) at bednight. Furthermore, the mean VAS at baseline and at end of treatment was 31.1 ± 31.7 and 6.6 ± 8.2, respectively, representing a more pronounced reduction (p = 0.042) at upon awaking. Vitality (VT) and mental health (MH) improved in overall chronic liver disease patients undergoing this therapy. VT domains of SF-36 was significantly altered by this treatment in HCC group (p=0.045).

Conclusions: This study demonstrated that nalfurafine hydrochloride improved pruritus in chronic liver disease patients, and more effective on the PRO in chronic liver disease patients with HCC.

Keywords: Nalfurafine hydrochloride, Short Form-36, Health-related quality of life, Hepatocellular carcinoma

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common malignancy worldwide and remains the third leading cause of cancer-related death in the last decade [1, 2]. Pruritus can occur at any stage of HCC in a local or generalized manner, and can significantly disturb daily life and disrupt sleep at night [3]. The pathophysiologic mechanism underlying pruritus is largely unknown, although cholestasis definitely plays a key role [4]. Therefore, new therapeutic approaches for the treatment of pruritus are strongly required. Neurotransmission involving opioid receptors is known to play a significant role in pruritus. Two opioid receptors are involved in pruritus signaling in the central nervous system; μ-receptors are stimulatory and κ-receptors are inhibitory. Nalfurafine hydrochloride is a selective κ-opioid receptor agonist that has been approved as an anti-pruritic drug in hemodialysis patients with refractory pruritus [5]. The efficacy and safety of nalfurafine hydrochloride was previously investigated in a phase 3 randomized double-blind trial involving 318 patients with chronic liver disease

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[6]. Pruritus, measured using the visual analog scale (VAS), was significantly decreased by week 4 of oral nalfurafine hydrochloride administration, and the safety issues were acceptable [6]. Furthermore, pruritus was measured by VAS only, and patient-reported outcomes (PRO) were not assessed using the short form 36 (SF-36). It is therefore unclear whether the efficacy of nalfurafine hydrochloride is influenced by clinical characteristics such as with/without of HCC. Very recently, a large-scale, postmarketing study was published, demonstrating the efficacy of nalfurafine hydrochloride [7]. Although this study employed 673 patients with chronic liver disease, about 10 % patients with HCC were included and the details of these patients were obscure in terms of PRO. The current study aimed to clarify whether the PRO of HCC patients with moderate to severe pruritus, measured using SF-36 and VAS, were improved by treatment with nalfurafine hydrochloride.

Patients and Methods

Screening of patients

We identified chronic liver disease patients with/without HCC who were experiencing moderate to severe pruritus, and invited them to participate in the current study. The pruritus screening procedure was designed as a separate observational cross-sectional study, which was approved by the Ethics Committee of Saiseikai Niigata Hospital.

We asked patients to complete questionnaires to assess their symptoms and HRQOL (the Japanese version of the SF-36), and assessed pruritus severity using the VAS. Patients were not invited to participate if they were being admitted to hospital, or had other comorbidities which were likely to affect their HRQOL. Pruritus and HRQOL assessment tools are SF-36 and VAS.

The SF-36 is a questionnaire used to measure general health status. In the SF-36, one item is designed to assess the perceived change in health status, and each of the remaining 35 items contributes to a score on one of eight scales: physical functioning; role-physical; bodily pain; general health perception; vitality; social functioning; role emotional; and mental health [8]. The Japanese version of SF-36 was already established and has been validated previously. Scores were calculated on the standard value (50 points) for the Japanese population [9, 10].

Nalfurafine hydrochloride intervention

Twenty-one patients with pruritus participated in the current interventional study of nalfurafine hydrochloride. Patients with moderate to severe pruritus who agreed to participate in the current study received once-daily oral nalfurafine hydrochloride (Toray Industries, Inc., Tokyo, Japan) at a dose of 2.5 μg. Pruritus severity and HRQOL were evaluated again at end of treatment using SF-36 and VAS. In patients receiving other anti-pruritic drugs such as bile acid sequestrates, anti-histamines, and moisturizing agents, the dosages of these were fixed throughout the study period and any additional treatments were prohibited.

Statistical Analyses

Continuous variables are presented as the mean ± the standard deviation if normally distributed. Comparisons between values at baseline and at end of treatment were performed using a paired Student's t test for continuous and normally distributed variables, and the Mann–Whitney U test for variables without normal distribution. Variation in the descriptive variables was assessed using Wilcoxon rank-sum test. A result was considered to be statistically significant when the P value was <0.05. Statistical analyses were performed using EZR ver. 1.37 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [11].

Results

Study participants

A total of 21 patients with pruritus agreed to participate in this interventional study, and their clinical characteristics are shown in Table 1. All participants were currently attending outpatient clinics.

Of 11 patients (5 male, 6 female; age 74.6 ± 6.5 years) were complicated HCC, other 10 patients (3 male, 7 female; age 75.6 ± 6.9 years) were not complicated HCC (Table 2).

Next, we assessed pruritus using VAS. The mean VAS at baseline and at end of treatment was 43.7±34.1 to 14.3±23.8 at bedtime, respectively, representing a more pronounced reduction (p=0.002) (Figure 1).

In HCC group, the mean VAS at baseline and at end of treatment was 46.8 ± 35.3 and 13.0 ± 19.4, respectively, representing a more pronounced reduction (p=0.009) (Figure 2a) at bednight.

Furthermore, the mean VAS at baseline and at end of treatment

Table 1: Clinical characteristics of the study participants at baseline

Variables	
Number of patients	21
Age (years)	75.1±6.7
Gender (Male: female)	8:13
Etiology (HBV/HCV/AIH/PBC/Alcohol/NASH/Others)	3/8/1/1/2/5/1
HCC (Presence: Absence)	11:10
VAS (at bednight)	43.7±34.1
VAS (upon awaking)	28.0±30.2

Table 2: Clinical characteristics of the study participants at baseline according to with/without HCC

Variables	With HCC	Without HCC	*P*-value
Number of patients	11	10	
Age (years)	74.6±6.5	75.6±6.9	0.725
Gender (Male: female)	5:6	3:7	0.689
Etiology (HBV/HCV/AIH/PBC/Alcohol/NASH/Others)	2/6/0/0/1/2/0	1/2/1/1/1/3/1	0.619
VAS (at bednight)	46.8±35.3	40.3±32.4	1.000
VAS (upon awaking)	31.1±31.7	24.7±28.2	0.696

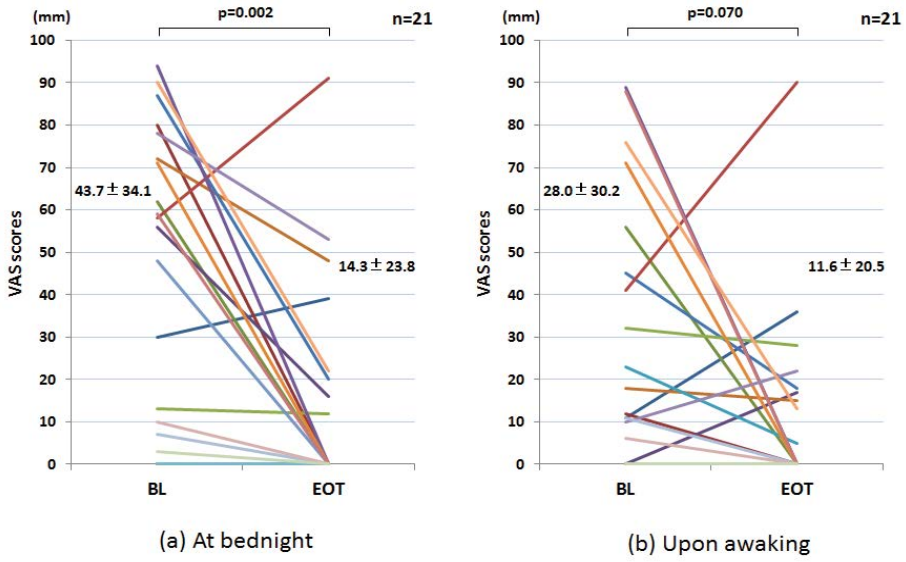


Figure 1: Visual analog scale assessment of pruritus severity in 21 patients with chronic liver disease. The VAS at baseline (BL) and at end of treatment (EOT) of nalfurafine hydrochloride are shown at bednight (a) and upon awaking (b).

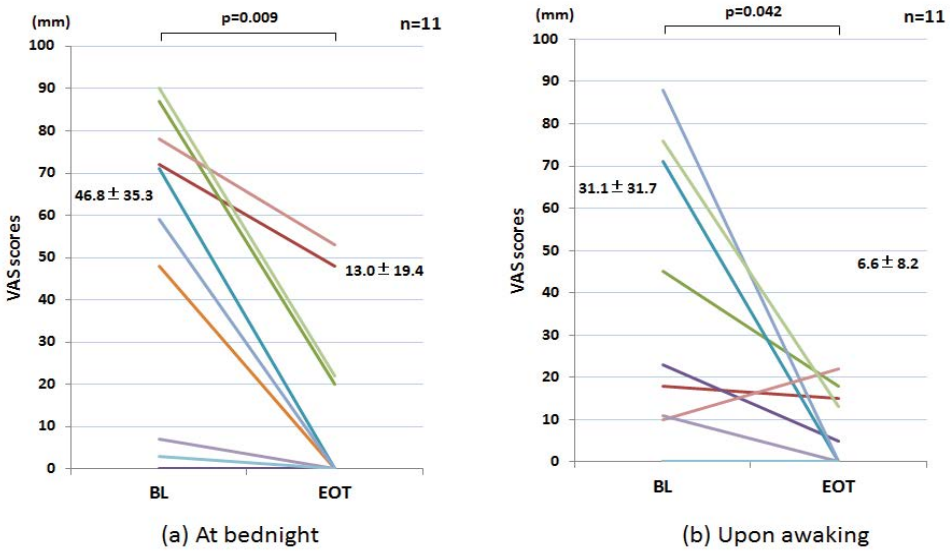


Figure 2: Visual analog scale assessment of pruritus severity in chronic liver disease with HCC patients. The VAS at baseline (BL) and at end of treatment (EOT) of nalfurafine hydrochloride are shown at bednight (a) and upon awaking (b).

was 31.1 ± 31.7 and 6.6 ± 8.2, respectively, representing a more pronounced reduction (p=0.042) (Figure 2b) at upon awaking.

Vitality (VT) and mental health (MH) improved in overall chronic liver disease patients undergoing this therapy. However, no significant changes in the courses of any SF-36 subscale were identified during therapy (Figure 3).

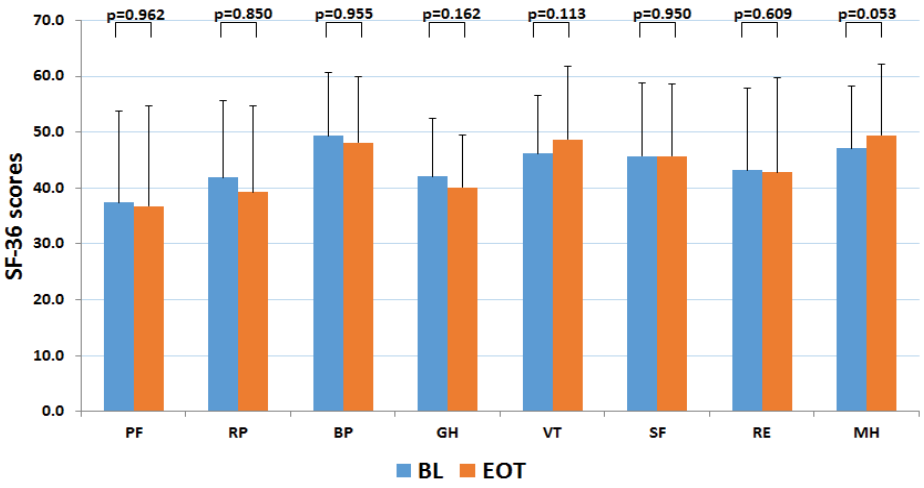
Regarding changes in HRQOL during therapy, the scores VT domain of the SF-36 were significantly altered by intervention with nalfurafine hydrochloride in HCC group (p=0.045) (Figure 4).

Discussion

Pruritus is most strongly associated with presence of hepatocellular carcinoma compared to other cancers [3]. Pruritus contributes to QOL impairment [12]. Patient-reported quality-of-life data are associated with motality of HCC [13].

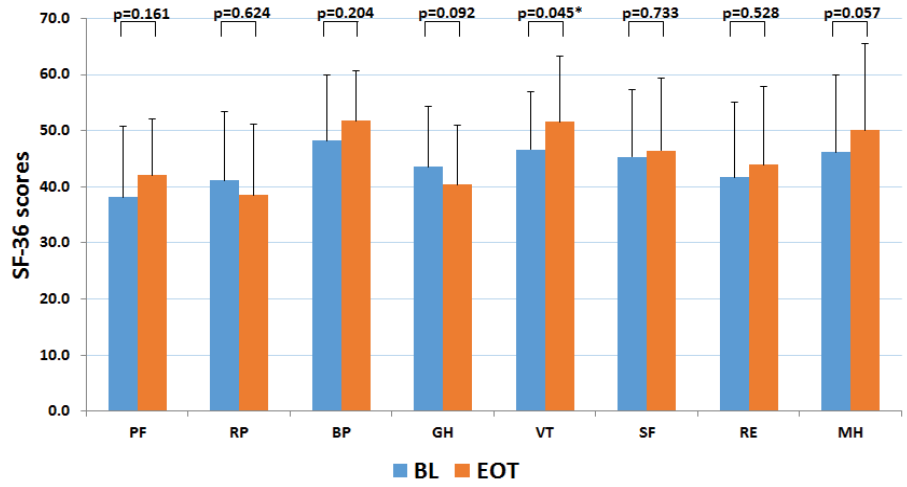
The current study investigated the efficacy of nalfurafine hydrochloride for pruritus in chronic liver disease patients with/without HCC. Most importantly, it examined whether an improvement of pruritus was linked to better PRO. The scores for VAS of all patients declined significantly following nalfurafine hydrochloride treatment, especially at bednight. The scores for VAS of HCC patients declined significantly following nalfurafine hydrochloride treatment at bednight as well as upon awaking.

The baseline SF-36 scores were 50, which is defined as the mean



PF: physical functioning, RP: Role-physical, BP: bodily pain, GH: General health perception, VT: Vitality, SF: Social functioning, RE: Role-emotional, MH: Mental health. The error bars represent standard deviations

Figure 3: The average score for each SF-36 domain at baseline (BL) and at end pf treatment (EOT) of nalfurafine hydrochloride treatment are shown. The error bars represent standard deviation.



PF: physical functioning, RP: Role-physical, BP: bodily pain, GH: General health perception, VT: Vitality, SF: Social functioning, RE: Role-emotional, MH: Mental health. The error bars represent standard deviations

Figure 4: The average score for each SF-36 domain at baseline (BL) and at end pf treatment (EOT) of nalfurafine hydrochloride treatment are shown in HCC patients. The error bars represent standard deviation.

of the general population. In this study, all of the baseline SF-36 scores less than 50 reflecting chronic liver disease. Vitality (VT) and mental health (MH) domains of SF-36 improved overall patients by administration of nalfurafine hydrochloride.

VT domains of the SF-36 scores significantly were altered by nalfurafine hydrochloride treatment of chronic liver disease with HCC. In this regard, we conclude that nalfurafine hydrochloride has some efficacy for the treatment of pruritus in patients with HCC, and that this effect was sufficient by QOL analysis. We should note, however, that treatment with nalfurafine hydrochloride was limited to end of treatment times in the current study and the PRO measured by other domains of SF-36 may be improved if the treatment will be continued much longer. Further study need to be confirmed in large-scale prospective studies.

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There are no conflicts of interest in the manuscript.

Declaration of personal and funding interests

None.

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References

1. Turdean S, Gurzu S, Turcu M, Voidazan S, Sin A (2012) Current data in clinicopathological characteristics of primary hepatic tumors. *Rom J Morphol Embryol* 53:719-724. [View Article]
2. Ozakyol A (2017) Global epidemiology of hepatocellular carcinoma (HCC Epidemiology). *J Gastrointest Cancer* 48:238-240. [View Article]
3. Larson VA, Tang O, Ständer S, Kang S, Kwatra SG (2019) Association between itch and cancer in 16,925 patients with pruritus: Experience at a tertiary care center. *J Am Acad Dermatol* 80:931-937. [View Article]
4. Beuers U, Kremer AE, Bolier R, Elferink RP (2014) Pruritus in cholestasis: facts and fiction. *Hepatology* 60:399-407. [View Article]
5. Kumagai H, Ebata T, Takamori K, Muramatsu T, Nakamoto H, et al. (2010) Effect of a novel kappa-receptor agonist, nalfurafine hydrochloride, on severe itch in 337 haemodialysis patients: a Phase III, randomized, double-blind, placebo-controlled study. *Nephrol Dial Transplant* 25:1251-1257. [View Article]
6. Kumada H, Miyakawa H, Muramatsu T, Ando N, Oh T, Tamamori K, et al. (2017) Efficacy of nalfurafine hydrochloride in patients with chronic liver disease with refractory pruritus: a randomized, double-blind trial. *Hepatol Res* 47:972-982. [View Article]
7. Akuta N, Kumada H, Fujiyama S, Kawamura Y, Sezaki H, et al. (2018) Predictors of pruritus in patients with chronic liver disease and usefulness of nalfurafine hydrochloride. *Hepatol Res* 48:45-50. [View Article]
8. Ware JEJ. The SF-36 health survey. In: Spilker B, editor. Quality of life and pharmacoeconomics in clinical trials. 2nd ed. Philadelphia: Lippincott-Raven; 1996. [View Article]
9. Fukuhara S, Bito S, Green J, Hsiao A, Kurokawa K (1985) Translation, adaptation, and validation of the SF-36 Health Survey for use in Japan. *J Clin Epidemiol* 51:1037-1044. [View Article]
10. Fukuhara S, Ware JE Jr, Kosinski M, Wada S, Gandek B (1998) Psychometric and clinical tests of validity of the Japanese SF-36 Health Survey. *J Clin Epidemiol* 51:1045-1053. [View Article]
11. Kanda Y (2013) Investigation of the freely available easy-to-use software 'EZR' for medical statistics. *Bone Marrow Transplant* 48:452-458. [View Article]
12. Ograczyk-Piotrowska A, Gerlicz-Kowalczuk Z, Pietrzak A, Zalewska-Janowska AM (2018) Stress, itch and quality of life in chronic urticaria females. *Postepy Dermatol Alergol* 35:156-160. [View Article]
13. Eilard MS, Hagström H, Mortensen KE, Wilsgaard T, Vagnildhaug OM, et al. (2018) Quality of life as a prognostic factor for survival in hepatocellular carcinoma. *Liver Int* 38:885-894. [View Article]

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