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Research Article

Regulative Effect by Fermented Herbal Derivatives for Prolonged Fatigue Monitored by Herpes Virus Copies in Human

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Abstract

Introduction: Prolong fatigue is a common among young and older adults, yet, only a small percentage of affected individuals seek medical attention. Several studies have described complementary and alternative medicine as effective strategies for improving fatigue. The aim of this study was to evaluate the effect of a fermented herbal derivatives (FHD) on prolonged fatigue lasting less than 12 months.

Methods: In this trial, participants with prolonged fatigue lasting 1 - 6 months were randomly allocated into two groups: experimental group (FHD group, n=10) and a control group (C group, n = 9). The FHD group consumed once a day for 9 months, whereas the control group did not. Outcomes were assessed at baseline, 3 month, 6 month and 9 month. The primary outcome was fatigue severity as measured by the gene copy of herpes simplex virus. Secondary outcomes included sleep quality, depression symptoms, and quality of life as measured by the Pittsburgh Sleep Quality Index, respectively.

Results: Of 20 individuals screened, 19 completed the study. The mean change in fatigue severity was significantly larger in the FHD group than in the C group at 6 months and improvements in fatigue severity were maintained at 9 month follow-up. Sleep quality was also significantly improved in the FHD group at 6 and 9 months. There were no statistically significant changes in depression, quality of life, or liver and renal parameters during the experimental period.

Conclusion: The present results suggest that the fermented herbal decoction reduces fatigue severity and improves sleep quality in both young and older ager with prolonged fatigue.

Keywords: *Fermented Herbal Decoction; Prolonged Fatigue; Herpes Simplex Virus*

Abbreviations

FHD: Fermented Herbal Decoction; CAM: Complementary and Alternative Medicine

We had been reported that FHD revealed many physiological effect after trials. For example, the intestinal flora were regulated by FHD on 2019. At 2020 we reported that FHD regulated fatigue condition together with the marker employed, cytokine and virus copies.

1. FHD reduced herpes virus copies in human.

2. FHD increased IL-1β for regulating fatigue condition.

3. FHD supported the deep sleeping emotion.
4. FHD enhanced the index FF/GAPHD that cooperated sleep times.
5. FHD contributed to the recovery of fatigue via brain topography.
6. These responses revealed by younger volunteers than older one.

Introduction

Prolonged fatigue refers to persistent or repeated episodes of clinically unexplainable fatigue that occur for a period lasting between one and six months. Prolonged fatigue is a common condition in the general population [1] while the prevalence of prolonged fatigue varies across communities and primary care settings, it is highly prevalent among working populations and young adults [2,3]. A Dutch Maastricht cohort study reported that 21.9% of working adults had prolonged fatigue [4]. Consistent with this finding, several studies have noted a high prevalence of chronic fatigue syndrome in young adults in their 30s and 40s [5-7]. Fatigue not only affects daily life and social as well as occupational functions but is also detrimental to health in the long term, implicated as a cause of chronic disease [8] and decreased quality of life [9,10]. Thus, prolonged fatigue is a condition that requires early prophylactic intervention and effective medical guideline by evidence based manner [11].

Fatigue is diagnosed based on subjective symptoms experienced by the patient due to a lack of clear clinical diagnostic criteria formulated based on physical examination or laboratory findings [12]. In conventional medicine, fatigue is treated with pharmacotherapy such as antidepressants or corticosteroids in order to mitigate or relieve symptoms that accompany fatigue; however, these medications are associated with various side effects [13]. Additionally, despite the fact that a considerable proportion of the population experience prolonged fatigue (estimated 41.2%), only a minority (7.6%) of individuals actually seek medical attention [14]. Accordingly, many people who experience fatigue have turned to complementary and alternative medicine (CAM), it was reported that 81.6% of people with fatigue symptoms use CAM, and 79.3% of people with prolonged fatigue in the United States use CAM [15]. Among various CAM methods, herbal teas have received substantial attention based on the fact that they are readily accessible over-the-counter and are generally perceived as safe [16]. In fact, a previous clinical trial reported that herbal teas significantly improved fatigue, sleep impairment and anxiety in the general population [17,18].

Purpose of the Study

The purpose of this trial was to conduct a pilot randomized clinical trial to assess the effects of an herbal tea containing medicinal plants used in TEAM on prolonged fatigue.

Accordingly, we hypothesized that an herbal tea containing these TEAM components would improve fatigue and related symptoms in young adults with prolonged fatigue.

Methods

Study design

A randomized clinical trial was conducted to compare the effects of an herbal tea between parallel groups (an intervention group and a control group). All participants underwent three assessments: baseline, end-of-treatment (four weeks after baseline), and follow-up (eight weeks after baseline/four weeks after treatment completion). The study was performed at the Kanazawa Medical University Hospital at Kanazawa between September 2019 and August 2020. The study was approved by the Institutional Review Board and informed consent was obtained from all participants prior to study participation. The protocol of this clinical trial was shown in m & M.

Participants

Participants were recruited and screened by questionnaire and interview. Eligible participants were working adults between the ages of 35 and 44, persistent or repetitive fatigue lasting 1 - 6 months and a score of at least 15 points on the Chalder Fatigue Scale [19]. Based on previous studies [20], the exclusion criteria were: presence of a primary sleep disorder; a diagnosis of depression within the past five years; a history of temperamental or mental cause of fatigue; individuals who took sleeping pills, antihistamines, or antidepressants in the 2 weeks prior to screening; individuals who received medical treatment for fatigue within the past one month; and individuals working night shifts or rotating shifts.

Randomization

Randomization was performed by a statistician prior to enrollment with an assignment ratio of 1:1 and a block size of 4. Participant group allocation information was sealed in individual opaque envelopes that were consecutively numbered for allocation concealment. After participant screening and completion of the baseline assessment, the envelopes were opened in consecutive order and participants were allocated into either a FHD group (E group) or a control group (C group). Participant blinding to group allocation was not possible due to the nature of the intervention.

Intervention

The herbal tea was specifically manufactured for the study by FHD Therapy by the sample presented by Echigo Yakusou Co. Ltd (Nigata Japan). Participants in the FHD group were given herbal tea sufficient for four weeks and a standard 15-ml daily at the baseline and began to drink the tea the following morning. Participants were instructed to infuse the teabag into hot water using the tumbler. Participants in the control group received no intervention during the eight weeks study period; however, they were offered the FHD with the same instructions upon study completion.

Statistical analysis

This study is a pilot study to determine the appropriate sample size required for a large-scale randomized clinical trial of herbal tea in individuals with prolonged fatigue. In a previous study that assessed the efficacy of a similar intervention, the minimum required sample size was 16 for each arm of the study [20]. In consideration of a 20% dropout rate, we calculated a sample size of 20 in each group. Data for continuous variables are presented as the mean and standard deviation. Categorical variables are presented as the frequency and percentage (%). Between-group differences at each visit were assessed using two-sample t-tests. Changes in measurements over time (baseline, after 4 weeks, after 8 weeks) within each group were analyzed with an analysis of variance, and the amounts of change over time (baseline, after 4 weeks, after 8 weeks) within each group were analyzed using paired t-tests. Effectiveness outcome variables were analyzed on an intention-to-treat basis including all randomized participants with at least one post-baseline assessment. Imputation was not used for missing data due to a small number of participants. For the safety evaluation, changes in liver and renal parameters were analyzed using paired t-tests. Additionally, all variables were screened for elevations of greater than 1.5-fold the upper limit of the reference range. A p-value of less than 0.05 was considered to be statistically significant. Statistical analyses were performed using SPSS 22.0 (IBM, Chicago, IL, USA).

Results

Virus Copie/HHV-6

We had selected the gene copies of herpes virus as an one of the vital maker of the fatigue (#). The number of the copies in senile (ave 74.1 yo) higher than the younger group (ave 38,1 yo). After administration of FHD, both groups down regulated, but drastic change was seen in younger than that of younger group (Figure 1).

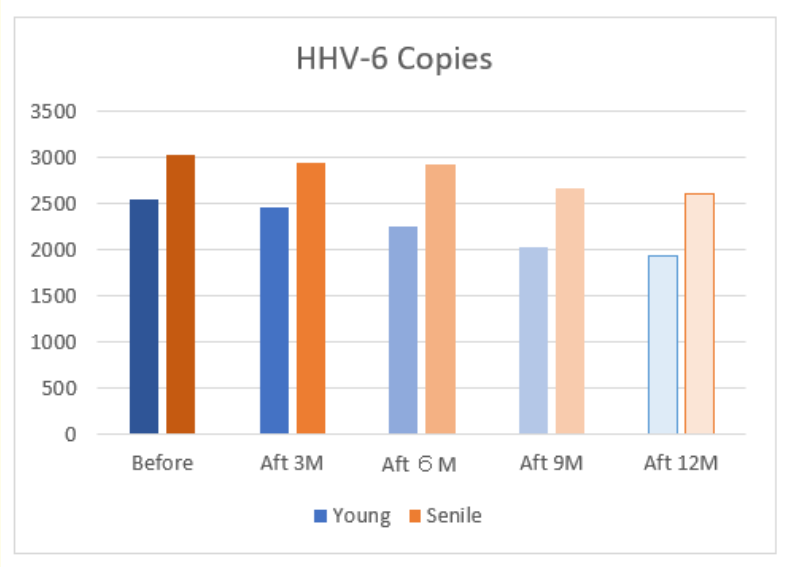

Figure 1

Dynamics of cytokine IL-1β

We tried to select cytokine IL-1β, as another marker of fatigue [21].

After informed consented to the volunteer, we tried to compared the cytokine IL-1β in the peripheral blood. For this marker, the serum level in senile (ave was 74.1 yo) higher than the younger group (ave 38,1yo) also. After administrated both senile and younger group, the both group were the same trend of small change after (Figure 2).

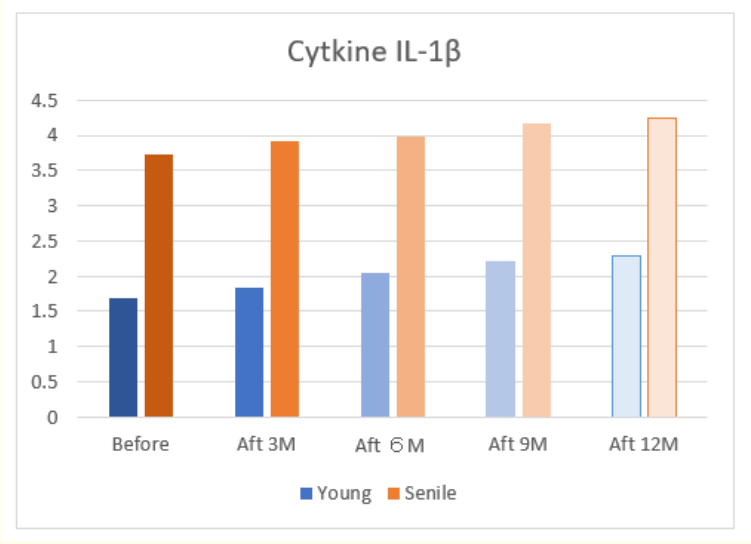

Figure 2

Sleep time and index FF/GAPDH

The final trial to show the fatigue of the volunteers, the index FF/GAPDH.

Was selected as a maker of fatigue. After start to compare, the level of younger group was clearly low, indicating they are vital compared than the senile. After administrating FHD, both group were downregulated according to the time factor. The pattern in both group was different. The younger group showed clear decedent in factor. However, senile one was not so clear decedent than the younger group (Figure 3).

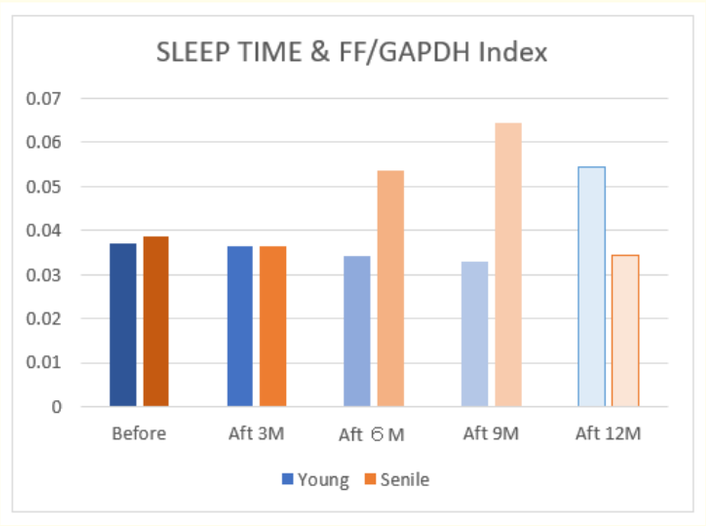

Figure 3

Quality of sleeping judge by brain topography

Final trial to show the pic up of brain blood change by topography. After start to compare, the level of younger group was clearly low, indicating they are vital compared than the senile. After administrating FHD, both group were downregulated according to the time factor. The pattern in both group was different. The younger group showed clear decedent in factor. Acceding to the figure 4, our results were showed by visual change by brain topography.

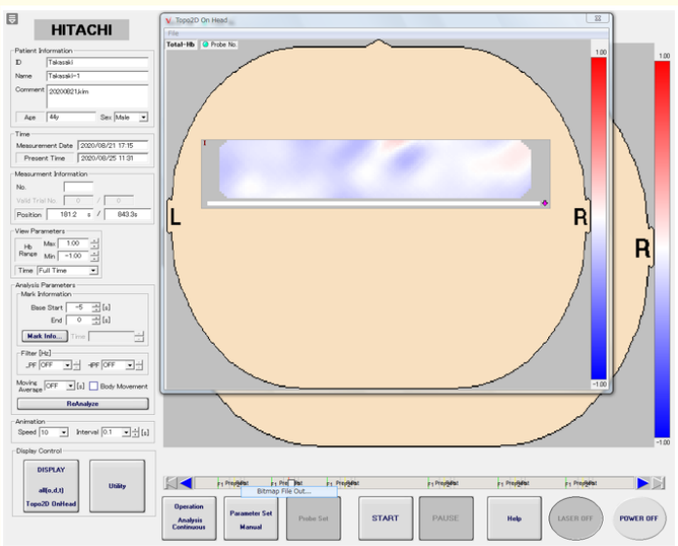

Figure 4a

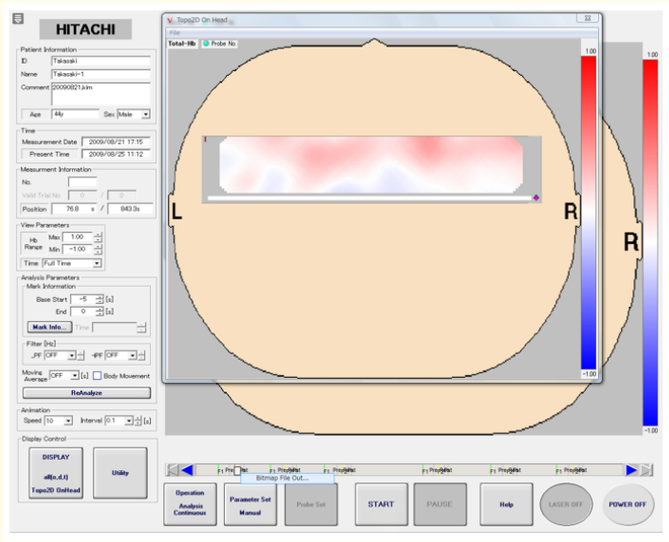

Figure 4b

Efficacy assessment brain topography

The compliance rates of all participants in the FHD who completed treatment were higher than 70% (range, 72.4 - 100%) so that all participants were considered compliant. The average compliance rate was 94.6%.

At the end of the four weeks treatment period, fatigue severity was significantly different between the FHD group, especially before and after over 3 months.

With regard to sleep quality, the young group showed over a 0.02-point decrease (improvement in sleep quality) between baseline and the four weeks assessment (P = 0.005) and a 1.2-point decrease between baseline and the twelve months follow-up, although the latter change was non-significant. The pretreatment group showed non-significant improvements in depression and quality of life. There were significant changes in assessment variables over time in the both group.

Safety assessment

No adverse events were reported during the study period. In the herbal tea group, there were no significant mean changes in liver or renal parameters between baseline and post-treatment, and no values were elevated greater than 1.5-fold the upper limit of the reference range.

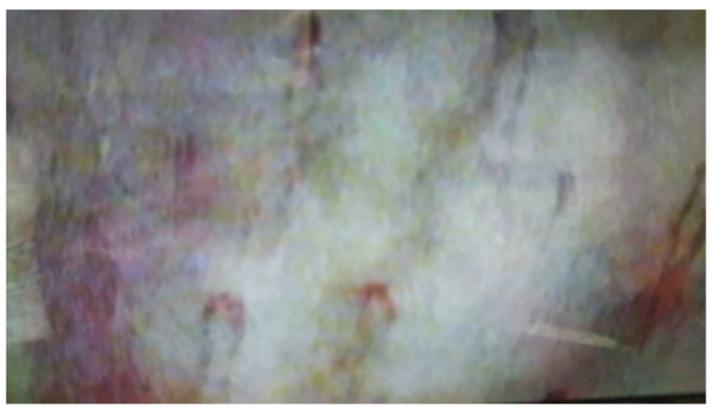

Figure 5a: *The capillary end of ring finger before FHD administration.*

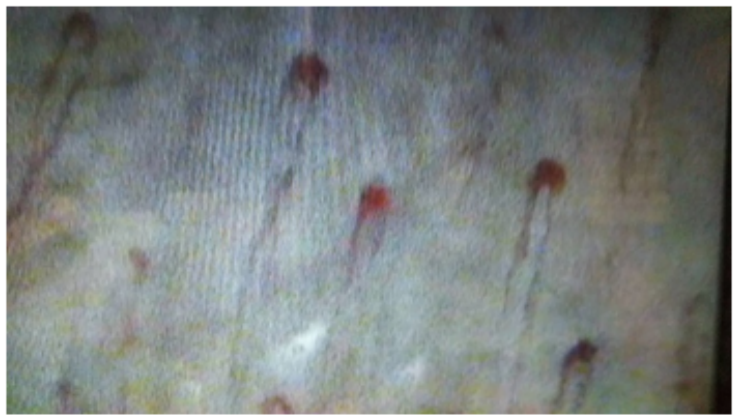

Figure 5b: *The capillary end of ring finger after 3 months later of FHD administration.*

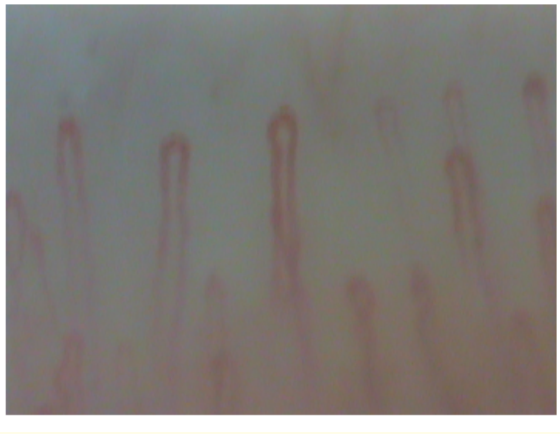

Figure 5c: *The capillary end of ring finger after 12 months later of FHD administration.*

Discussion

In this randomized clinical trial, we compared and analyzed the effects of an herbal tea regimen on prolonged fatigue in young adults. Our results showed that the T group had significant reductions in fatigue severity after the herbal tea intervention, and improved fatigue in the T group were significantly different from that in the C group. The Chalder Fatigue Scale score for the T group immediately after the four weeks herbal tea intervention was 13 points, as compared to 18 points in the control group. The recommended cutoff score on the Chalder Fatigue Scale to distinguish individuals with chronic fatigue syndrome from healthy individuals is 14.5 points [22]; based on this cutoff, we can infer that the herbal tea regimen lowered participants' perceived fatigue to a level close to that in healthy individuals. Furthermore, improvements in fatigue were maintained four weeks after completion of the intervention, suggesting that the herbal tea used in this study produced lasting beneficial effects in individuals with prolonged fatigue. In another study, four-week treatment of individuals with chronic fatigue with a tea containing Astragali Radix, one of the ingredients in our herbal tea, led to a 50% reduction in fatigue rated using a visual analog scale [23], similar to improvements observed in our study. It is difficult to draw generalized conclusions given

differences in individual participant characteristics and herbal tea compositions, but these results suggest that herbal teas can improve recurrent fatigue.

Fatigue is accompanied by various physical and psychological symptoms, including depression and sleep impairment [24]. In the present study, herbal tea treatment also produced improvements in sleep quality; PSQI scores in the T group decreased from 8 points to 6 points after the four weeks intervention, suggests that herbal teas can also improve sleep problems that commonly accompany fatigue. Additionally, improvements in sleep quality were still evident at four weeks after treatment completion, similar to the pattern observed for improvements in fatigue. Yet, it is notable that good sleep quality is considered to be a PSQI score below 5 points [25], whereas improvements in our study did not achieve this value. Nonetheless, these data highlight he potential utility of herbal teas for treating sleep disturbances accompanying fatigue. Future studies more closely evaluate the effects of herbal teas on fatigue-related sleep problems.

The T group tended to show improvements in depression, but not to a significant degree. We believe that as a pilot study, the intervention period was too short and the sample size was too small to examine statistically significant changes in depression. In a previous study, sixth-month FHD in 20 patients with chronic fatigue syndrome-like illness led to beneficial effects on fatigue and depression symptoms compared to control subjects [33], whereas a similar study failed to identify significant improvements in depression symptoms using a shorter intervention period (12-months FHD) and smaller sample size (n = 20) [26]. In the present study, the average BDI score in the T group decreased from 11 points at baseline to 7 - 8 points after the intervention, representing a transition from mild depression to a non-depressed state as per Becks' criteria [27]. Thus, this pilot study provides a proof-of-concept and allows the calculation of a minimum required sample size for a future large- scale clinical trial investigation. Lastly, we did not identify significant changes in quality of life after the four weeks herbal tea intervention; we speculate that this was due to the fact that participants in our study did not have chronic fatigue and thus the mean EQ-5D score was above 0.9 points at the baseline, indicating good health status in terms of daily living functions.

Further, the ultimate objective of this study was to calculate the minimum sample size required in large clinical trials in the future. In consideration of intergroup differences in the primary outcome of the study, we found that 18 participants were required for each group for a 5% significance level (alpha) and 80% power (beta).

Several reports describe CAMs as effective strategies for reducing fatigue. A systematic review of randomized controlled trials of various CAMs in patients with fatigue revealed that qigong, massage and tuina have positive effects on fatigue [28]. Yet, most of the interventions used in these studies required help from professional health providers. CAM is growingly worldwide as an important modality for treating and preventing disease [29], in part due to the fact that CAM promotes empowerment and self-help, increasing people's satisfaction as they actively participate in the management of their own health [30]. Therefore, herbal teas, which can be used without the assistance of a professional and are both familiar and easily accessible, may be preferred over professional medical for treating mild issues such as prolonged fatigue. Moreover, considering that only a minority of people with fatigue express their symptoms to a medical professional and consider treatment [31], herbal teas may represent an attractive alternative for these patients.

The present study had several limitations. First, as aforementioned, this study included a small sample size, which limited the study's statistical power. This is because this study was designed as a preliminary investigation to lay the foundation for a future, larger-scale study. Second, participants could not be blinded due to the nature of the intervention, which may have lead to an overestimation of the intervention's effectiveness. This is because the tea used in this study was unique in its color and flavor, which complicated placebo design for the control group. In future studies, comparison with other widely used treatment modalities and the use of objective outcome measures to complement subjective assessments of fatigue should be considered to evaluate the clinical value of herbal tea. Finally, our herbal tea was obtained from three plant sources, such that there were numerous active components potentially mediating the observed efficacy in prolonged fatigue. It will be useful in future studies to identify these active compounds and obtain pharmacokinetic data.

Conclusion

This small pilot study found that drinking a eighty component FHD daily for four weeks improved the level of fatigue in young adults with prolonged fatigue. The herbal FHD intervention also significantly improved sleep quality, which is a common issue accompanying fatigue. We expect subsequent larger-scale clinical trials to substantiate the benefits of FHD for prolonged fatigue and inform the exact mechanisms underlying its observed efficacy.

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