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Safety and Efficacy of Gamma-Aminobutyric Acid from Fermented Rice Germ in Patients with Insomnia Symptoms: A Randomized, Double-Blind Trial

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Background and Purpose This study aimed to determine the subjective and objective improvements in sleep quality after treatment with gamma-aminobutyric acid (GABA; 300 mg daily) extracted from unpolished rice germ.

Methods This study was a prospective, randomized, double-blind, and placebo-controlled trial. In total, 40 patients who complained of insomnia symptoms were enrolled and randomly assigned to the GABA treatment group (n=30) or the placebo group (n=10). Polysomnography was performed, and sleep questionnaires were administered before treatment and after 4 weeks of treatment.

Results After 4 weeks of treatment the sleep latency had decreased [13.4±15.7 min at pretreatment vs. 5.7±6.2 min at posttreatment (mean±SD), p=0.001] and the sleep efficacy had increased (79.4±12.9% vs. 86.1±10.5%, p=0.018) only in the GABA treatment group. Adverse events occurred in four subjects (10%).

Conclusions This study shows that treatment with unpolished-rice-germ-derived GABA improved not only the subjective sleep quality but also the objective sleep efficacy without severe adverse events.

Key Words gamma-aminobutyric acid, fermented rice germ extract, insomnia, treatment.

INTRODUCTION

The pharmacological treatment of insomnia usually employs a benzodiazepine receptor agonist that affects gamma-aminobutyric acid (GABA)-ergic transmission.[1,2] Benzodiazepine receptor agonists increase the binding of GABA to $GABA_A$ receptors and enhance inhibitory signals to cell groups that promote arousal—these actions decrease sleep latency and increase sleep continuity.[3] However, the use of such agonists is often restricted by the risks of overdose, tolerance, and addiction.[4] Additionally, benzodiazepine receptor agonists often have adverse effects, such as daytime sedation, delirium, ataxia, anterograde memory disturbance, and sleep-related behaviors.[5] The high prevalence of insomnia (e.g., 25% of the US population)[6] highlights the importance of identifying safer substances for improving sleep quality.

GABA exists naturally in many types of foods.[7,8] There are low amounts of natural GABA in rice (1−40 mg/100 g), unpolished rice (4−8 mg/100 g), and fermented unpolished rice (10−100 mg/100 g), while much higher GABA concentrations can be produced by using *Lactobacillus brevis* or *Lactococcus lactis*.[9,10] Natural GABA extracts can also have a hypnotic effect and increase sleep efficacy. These effects have been evaluated in both animals[11,12] and

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humans,[13,14] but these studies evaluated only subjective sleep quality based on self-reported questionnaires. Therefore, the effects of natural-GABA intake on sleep structure and sleep efficacy remain to be fully and objectively elucidated.

This study aimed to objectively determine the effect of natural-GABA intake on sleep by using serial polysomnography (PSG). We performed a randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of natural GABA derived from fermented rice germ extract at a daily dose of 300 mg.

METHODS

Participants

Adult patients (older than 18 years) with one or more symptoms of insomnia (difficulty initiating sleep, difficulty maintaining sleep, or early-morning awakening) during the previous month were considered for inclusion in the study. To properly evaluate the efficacy of fermented rice germ extract containing GABA (RFE-GABA), we included patients who had a decrease in sleep quality [more than 5 points on the Pittsburgh Sleep Quality Index (PSQI)[15]] and who had insomnia symptoms [more than 8 points on the Insomnia Severity Index (ISI)[16]]. Patients were excluded if they had 1) cognitive dysfunction defined as a Mini Mental State Examination score of less than 24, 2) comorbid psychiatric disorders [severe depression with a Beck Depression Inventory (BDI) score ≥29 or severe anxiety with a Beck Anxiety Inventory (BAI) score of ≥30], neurological disorders, or other sleep disorders, or 3) severe medical illness, or 4) performed shift work, or 5) took medication (e.g., hypnotics or sedatives) that could affect sleep. This study was approved by the Institutional Review Board of Kyung Hee University Hospital at Gangdong (IRB No. 2015-11-006). Written informed consent to participate was obtained from all of the enrolled patients.

Procedures

This study used natural GABA as manufactured by Natural Way (Pocheon, Korea) using a method modified from that used in a previous study.[17] In brief, *Lactobacillus sakei* B2-16 was cultivated in fermented rice germ extract medium containing 4% sucrose, 1% yeast extract, and 7% monosodium glutamate; this process produced RFE-GABA containing 15% GABA. Previously we found that high-dose GABA (300 mg daily) improved subjective insomnia symptoms better than lower-dose GABA (150 mg daily) and did not cause severe adverse events.[18] In the present study we therefore used RFE-GABA containing 300 mg of GABA. Maltodextrin was used as a vehicle for the RFE-GABA and placebo tablets (which had an identical appearance).

Procedures

The patients were randomly assigned at a ratio of 3:1 to receive an RFE-GABA or placebo tablet at 1 hour before sleeping. Each patient completed questionnaires evaluating sleep (PSQI and ISI), depression (BDI), and anxiety (BAI), and underwent standard overnight PSG. PSG, PSQI, and ISI evaluations were repeated at 4 weeks after RFE-GABA treatment or placebo. PSG was performed using a digital polygraph system version 2.6 (Grass-Telefactor Twin, West Warwick, RI, USA). The data were scored manually according to version 2.0 of the American Academy of Sleep Medicine Manual for the Scoring of Sleep and Associated Events.[19]

Outcomes

The primary end point was a change in PSG sleep latency at 4 weeks after RFE-GABA treatment or placebo. Secondary end points were changes in sleep efficiency, sleep structure, and sleep questionnaire scores, including on the PSQI and ISI. Safety end points were any adverse events. Adverse events were defined as any unintended response thought to be related to treatment. The Common Terminology Criteria for Adverse Events (version 3.0)[20] was used to grade the events, with severe adverse events defined as having a grade of 3 or higher.

Statistical analysis

The Mann-Whitney U test was used to evaluate group differences for continuous variables, including demographics, questionnaire scores, and PSG parameters. Categorical variables were compared using the chi-square test. Repeated-measures analysis of variance (ANOVA) with the treatment group (placebo vs. RFE-GABA) as the between-subject factor and time (baseline vs. 4 weeks after treatment) as the within-subject factor was used to test for an overall group difference in the treatment effects. Mauchly's sphericity test for measuring homoscedasticity and compound symmetry was applied. A multivariate test using Wilks' lambda was used when the assumption of sphericity was not satisfied ($p<0.05$). The changes from baseline to 4 weeks after the treatment were also compared between the treatment groups using the Wilcoxon signed-rank test. The significance cutoff was set to 0.05. All statistical comparisons were performed with SPSS version 22.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Patient characteristics

In total, 43 patients with symptoms of insomnia were initially enrolled, of which 3 were excluded because they had severe sleep apnea. Thirty of the remaining patients were random-

ized to receive RFE-GABA, while the other 10 patients received the placebo. The patients were aged 49±14 years (mean±SD), and one-quarter of them were male. The RFE-GABA treatment and placebo groups were well matched for age, sex, and PSQI, ISI, BDI, and BAI scores. Baseline PSG showed an increased proportion of N1 sleep and increased arousal index values in the RFE-GABA treatment group compared with those in the placebo group (p=0.022 and 0.042, respectively) (Table 1).

PSG changes after 4 weeks of treatment

Repeated-measures ANOVA revealed a significant time effect for N2 sleep [F(1, 38)=5.592, p=0.023]. However, the Mann-Whitney U test for individual groups showed no significant change between before and 4 weeks after the treatment. A significant interaction between group and time was found only for sleep latency [F(1, 38)=7.510, p=0.009]. The Mann-Whitney U test revealed a significant decrease in sleep latency only in the RFE-GABA treatment group (13.4±15.7 and 5.7±6.2 min in the pre- and posttreatment groups, respectively; p<0.0001). In contrast, there was no such change in the placebo group (p=0.646) (Table 2).

Table 1. Demographics variables and questionnaire and PSG results at baseline

	Placebo (n=10)	RFE-GABA (n=30)	p
Age (years)	47.2±16.8	50.2±12.8	0.584
Sex (male)	4 (40.0)	6 (20.0)	0.232
PSQI (total score)	11.0±2.4	11.0±2.2	0.962
C1 (sleep quality)	1.8±0.6	2.0±0.5	0.369
C2 (sleep latency)	2.3±0.7	2.3±0.8	0.904
C3 (total sleep time)	2.1±0.7	2.4±0.8	0.246
C4 (sleep efficacy)	1.6±0.7	1.5±1.1	0.655
ISI	16.9±4.2	14.6±4.6	0.125
BDI score	9.2±7.8	11.1±5.3	0.178
BAI score	8.9±3.0	10.7±6.4	0.650
PSG			
Total sleep time	331.7±46.4	312.0±52.1	0.241
N1 sleep (%)	9.4±4.7	15.2±7.5	0.022
N2 sleep (%)	38.2±11.5	36.7±8.1	0.333
N3 sleep (%)	34.6±9.3	31.8±9.7	0.341
REM sleep (%)	17.8±5.0	16.3±6.8	0.553
WASO (min)	57.4±42.9	65.0±46.8	0.532
Sleep latency	7.0±4.9	13.4±15.7	0.574
REM sleep latency	109.3±42.3	125.0±78.1	0.743
Sleep efficacy	83.9±10.7	79.4±12.9	0.333
Arousal index	17.6±8.5	28.0±14.1	0.042
AHI	2.4±5.3	7.6±12.6	0.077
RDI	6.1±7.3	11.6±14.1	0.288

Data are mean±SD or n (%) values.
AHI: apnea-hypopnea index, BAI: Beck Anxiety Inventory, BDI: Beck Depression Inventory, ISI: Insomnia Severity Index, PSG: polysomnography, PSQI: Pittsburgh Sleep Quality Index, RDI: respiratory distress index, REM: rapid eye movement, RFE-GABA: fermented rice germ extract containing gamma-aminobutyric acid, WASO: wake after sleep onset.

Changes in sleep questionnaire scores after 4 weeks of treatment

Repeated-measures ANOVA revealed significant time effects for all questionnaire scores with the exception of component C4 of the PSQI. The Mann-Whitney U test for individual groups showed decreases in the PSQI total score (from 11.0±2.2 at pretreatment to 9.8±2.5 at posttreatment, p=0.003), PSQI components C1 and C3 (p=0.002 and 0.004, respectively), and ISI (14.6±4.6 at pretreatment to 11.5±4.3 at posttreatment, p<0.0001) in the RFE-GABA group. No significant changes were found in the PSQI scores in the placebo group, with the exception of a decrease in component 3 (p=0.025). However, no significant effects on groups or significant interactions between group and time were found (Table 2).

Adverse events

Four subjects (10%) experienced an adverse event: three (10%) from the RFE-GABA treatment group and one (10%) from the placebo group. Three patients in the RFE-GABA treatment group complained of mild abdominal discomfort (n=2), headache (n=1), and drowsiness (n=1), and the single patient in the placebo group reported drowsiness (n=1). All of the adverse events were classified as either grade 1 or 2 (mild to moderate).

DISCUSSION

Sleep latency was significantly reduced for RFE-GABA intake compared to placebo intake. RFE-GABA intake also improved subjective sleep quality and reduced the symptom severity in subjects with insomnia; moreover, it induced only minor side effects. This study suggests that patients who suffer from insomnia can benefit from RFE-GABA intake without suffering severe adverse events.

RFE-GABA can affect sleep by enhancing central GABAergic neurotransmission. GABA is a major inhibitory neurotransmitter in the central nervous system that is well known to be involved in sleep physiology. Multiple populations of GABAergic neurons are involved in the regulation of non-rapid-eye-movement (REM) and REM sleep.[21,22] Increasing the level of GABA may both naturally induce and help to maintain sleep. Previous studies found hypnotic effects of GABA in both animals[3] and healthy humans.[23] In agreement with these studies, GABA supplementation in the present study significantly reduced sleep latency in patients with insomnia. How-

Table 2. Repeated-measures analysis of variance results for the time effect and the interaction effect between time and group of RFE-GABA treatment

	Placebo		RFE-GABA		Time effect*	Time×group effect†
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	F (*p*)	F (*p*)
PSG						
Total sleep time	331.7±46.4	312.1±50.5	312.0±52.1	320.6±55.7	ns	ns
N1 sleep (%)	9.4±4.7	9.3±5.6	15.2±7.5	12.6±8.8†	ns	ns
N2 sleep (%)	38.2±11.5	37.4±11.8	36.7±8.1	35.9±8.4	5.592 (0.023)	ns
N3 sleep (%)	34.6±9.3	35.0±9.1	31.8±9.7	33.3±11.8	ns	ns
REM sleep (%)	17.8±5.0	18.1±4.8	16.3±6.8	18.3±6.8	ns	ns
WASO (min)	57.4±42.9	42.6±37.4	65.0±46.8	45.4±47.0†	ns	ns
Sleep latency	7.0±4.9	15.2±24.6	13.4±15.7	5.7±6.2§	ns	7.510 (0.009)
REM sleep latency	109.3±42.3	115.7±70.0	125.0±78.1	105.0±67.9	ns	ns
Sleep efficacy	83.9±10.7	84.5±13.0	79.4±12.9	86.1±10.5†	ns	ns
Arousal index	17.6±8.5	17.9±7.7	28.0±14.1	25.2±14.6	ns	ns
AHI	2.4±5.3	3.1±6.6	7.6±12.6	8.1±13.0	ns	ns
RDI	6.1±7.3	7.6±8.3	11.6±14.1	12.7±15.8	ns	ns
PSQI (total score)	11.0±2.4	9.9±2.6	11.0±2.2	9.8±2.5§	9.031 (0.005)	ns
C1 (sleep quality)	1.8±0.6	1.5±0.7	2.0±0.5	1.4±0.6§	8.398 (0.006)	ns
C2 (sleep latency)	2.3±0.7	1.8±0.8	2.3±0.8	2.1±0.8	5.725 (0.022)	ns
C3 (total sleep time)	2.1±0.7	1.6±0.8	2.4±0.8	1.9±1.0§	13.338 (0.001)	ns
C4 (sleep efficacy)	1.6±0.7	1.4±1.2	1.5±1.1	1.3±1.0	ns	ns
ISI	16.9±4.2	12.9±6.8	14.6±4.6	11.5±4.3§	16.076 (<0.0001)	ns

Data are mean±SD or *n* (%) values. Groups: RFE-GABA vs. placebo, times: baseline vs. 4 weeks after treatment.
*within-groups comparison, †between-groups comparison, †$p<0.05$, §$p<0.01$, Wilcoxon signed-rank test for each group.
AHI: apnea-hypopnea index, ISI: Insomnia Severity Index, ns: not significant, PSG: polysomnography, PSQI: Pittsburgh Sleep Quality Index, RDI: respiratory distress index, REM: rapid eye movement, RFE-GABA: fermented rice germ extract containing gamma-aminobutyric acid, WASO: wake after sleep onset.

ever, some studies have found that GABA does not cross the blood-brain barrier (BBB),[24] although others found that small amounts of GABA did cross the BBB.[25,26] Although we did not measure GABA in the cerebral spinal fluid, the results of our study suggest that natural-GABA intake can inhibit neurons that promote arousal.

RFE-GABA may also reduce insomnia symptoms by stabilizing mood. Several epidemiological studies have found strong associations between insomnia and psychiatric disorders,[27,28] and reduced GABA activity is reportedly present in several neuropsychiatric disorders, including anxiety and depression.[29] The up-regulation of $GABA_A$ receptors can reduce anxiety symptoms and exert antipanic effects.[30,31] Additionally, an electroencephalography study showed that oral GABA supplements decreased beta waves, which is indicative of relaxation.[7] The anxiolytic effect of RFE-GABA may result in a subjective improvement in sleep quality and symptoms, as shown in our patients.

Sedative hypnotics that target GABAergic transmission are known to decrease slow-wave sleep and inhibit REM sleep.[22,32,33] However, RFE-GABA intake did not affect the sleep structures in our study. The preservation of slow-wave sleep and REM sleep is an advantage of RFE-GABA treatment over treatment with conventional hypnotic drugs. Another limitation of sedative hypnotics is that the side effects are dose-related.[5] RFE-GABA tablets containing 300 mg of GABA were safe and caused only minor adverse events, which included mild gastrointestinal discomfort and headache. Only two patients (5%) reported drowsiness, which has been a major limitation of sedative hypnotics.

This study was subject to several limitations. A major limitation was the small number of patients in the placebo group. Also, the baseline sleep characteristics differed between the placebo and RFE-GABA groups. Although this was a single-center study that included only a small number of placebo controls, this is the first randomized placebo-controlled trial to use serial PSG to objectively evaluate the efficacy of natural GABA in subjects with insomnia. Additional studies involving larger numbers of patients and longer follow-up periods may be warranted to evaluate the long-term dependency, cognitive influence, and tolerance of RFE-GABA.

In conclusion, the findings of this study suggest that RFE-GABA can be used to reduce sleep latency and improve subjective sleep quality without serious adverse effects. Because it is a naturally extracted substance without severe adverse events, RFE-GABA may be widely administered as a supplement to

improve sleep health in the general population. Further studies with longer follow-up periods are necessary to determine the long-term safety of RFE-GABA.

Conflicts of Interest

The authors have no financial conflicts of interest.

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