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Efficacy and Safety of Low-Dose Gamma-Aminobutyric Acid From Unpolished Rice Germ as a Health Functional Food for Promoting Sleep: A Randomized, Double-Blind, Placebo-Controlled Trial

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Dear Editor,

Gamma-aminobutyric acid (GABA)-enriched fermented foods have the potential to ameliorate insomnia because of their inhibitory action on the central nervous system.[1] As functional foods, they are safe for oral intake, easily accessible, and can relieve anxiety and elevate mood.[2]

We previously demonstrated that 4 weeks of natural GABA extracts (300 mg daily) can improve both subjective sleep quality and objective sleep efficacy.[3] Natural-GABA treatment reduced sleep latency and improved sleep questionnaire scores. However, two out of forty patients complained of abdominal discomfort, and one patient complained of headache after receiving the natural-GABA treatment. Also, since insomnia often requires long-term therapy, the adverse effects may have been underestimated. Accordingly, in the present study we explored whether low-dose natural GABA (75 mg) is as effective in improving sleep quality and sleep efficacy as is high-dose natural GABA (300 mg), and without adverse events.

This study performed a double-blind, randomized, placebo-controlled trial of low-dose natural GABA (75 mg) in patients with insomnia. The study design was equivalent to that of our previous study.[3] The primary outcome was the changes in overnight polysomnography (PSG) sleep latency and sleep efficacy between baseline and after 4 weeks in the GABA-treatment population. The secondary endpoints were changes in other PSG parameters and sleep questionnaire scores between baseline and 4 weeks.

Differences between the study groups at baseline were assessed using either the chi-square or Fisher's exact test for categorical data, and the *t*-test for continuous data. Changes from baseline to 4 weeks after treatment in each treatment group were determined using the Wilcoxon signed-rank test.

This study screened 64 patients between September 18, 2018 and July 21, 2020. Ten individuals were excluded because they withdrew their consent before randomization. The remaining 54 patients were randomly allocated to receive either natural GABA (n=26) or a placebo (n=28), among whom 50 (25 natural GABA and 25 placebo) completed the study. Two of the participants (one from the control group and the other from the natural-GABA group) dropped out because they did not complete follow-up PSG, and two others dropped out from the control group because they withdrew their consent. The demographics did not differ significantly between the two groups. The mean age of the participants was 46 years, and 24% of them were male.

Sleep latency decreased after 4 weeks of natural-GABA treatment (from 9.0±12.6 min [mean±SD] at pretreatment to 4.8±4.6 min at posttreatment, p=0.0038), but the changes

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Table 1. Variance PSG results and sleep questionnaire results for the time effect and the interaction effect between time and group of natural GABA treatment

	GABA (*n*=25)		*p*-value†	Placebo (*n*=25)		*p*-value†	*p*-value*
	Pretreatment	Posttreatment		Pretreatment	Posttreatment		
PSG							
Total sleep time (min)	313.8±61.1	326.8±61.1	0.0681	306.5±71.4	295.5±58.7	0.1883	0.0213
Sleep latency (min)	9.0±12.6	4.8±4.6	0.0038	6.5±3.9	8.2±7.9	0.7603	0.0240
Sleep efficacy (%)	86.5±12.2	88.0±9.8	0.2972	84.5±12.6	86.9±10.3	0.5851	0.6903
WASO (%)	11.3±10.7	10.3±9.4	0.5787	13.7±12.5	10.6±10.0	0.3568	0.7751
N1 sleep (%)	19.8±8.6	21.2±11.2	0.9272	19.5±11.8	18.8±10.9	0.4607	0.7032
N2 sleep (%)	54.7±9.4	49.4±10.8	0.0041	52.1±10.0	52.5±11.9	0.6099	0.0291
N3 sleep (%)	8.6±6.4	12.9±7.6	0.0043	9.5±8.1	8.2±6.1	0.1015	0.0003
REM sleep (%)	16.9±6.1	16.6±7.1	0.8448	18.9±7.3	20.5±6.4	0.8142	0.9173
AHI (/h)	4.7±6.9	4.5±7.3	0.5503	3.1±3.8	3.2±3.7	0.6056	0.4055
PLMI (/h)	4.5±12.9	4.5±14.3	0.8438	5.7±15.3	7.2±23.2	0.6636	0.9442
Arousal index (/h)	22.9±9.8	21.1±11.4	0.0316	20.9±11.1	21.2±8.2	0.4545	0.0213
Sleep questionnaire							
PSQI total	11.2±2.4	8.7±3.0	<0.0001	10.3±2.9	8.3±2.8	0.0020	0.7135
ESS	8.42±4.6	6.5±4.2	0.8820	8.3±3.0	7.4±3.4	0.4537	0.4709
ISI	15.3±4.5	10.4±5.3	<0.0001	12.8±5.0	10.4±5.2	0.0002	0.0419

Data are mean±SD.
*Compared between groups difference: *p*-value by Wilcoxon rank sum test; †Compared within groups (posttreatment vs. pretreatment): *p*-value by Wilcoxon singed rank test.
AHI, Apnea-Hypopnea Index; ESS, Epworth Sleepiness Scale; GABA, gamma-aminobutyric acid; ISI, Insomnia Severity Index; PLMI, Periodic Limb Movement Index; PSG, polysomnography; PSQI, Pittsburgh Sleep Quality Index; REM, rapid eye movement; WASO, wake after sleep onset.

were not significant relative to the placebo. Sleep efficiency did not differ significantly between before and after treatment in both groups. The proportion of N2 sleep decreased from pretreatment to posttreatment (54.7%±9.4% versus 49.4%±10.8%, p=0.0041), as did the arousal index (22.9%±9.8%/h versus 21.1%±11.4%/h, p=0.0316), while the proportion of N3 sleep increased (8.6%±6.4% versus 12.9%±7.6%, p=0.0043) only in the natural-GABA-treatment group. Both the natural-GABA and control groups showed decreases in Insomnia Severity Index and Pittsburg Sleep Quality Index scores (Table 1). No adverse events were reported.

This study has revealed that low doses (75 mg) of natural GABA are effective in the treatment of sleep disorders. Sleep latency decreased only in the GABA-treatment group, suggesting that GABA has hypnotic effect. In addition, N3 sleep increased and the arousal index decreased in the natural-GABA-treatment group but not in the control group.

Patients treated with low-dose natural GABA (75 mg) exhibited a reduction in sleep latency, as also found in a previous study for high-dose natural GABA (300 mg).[3] However, unlike high-dose natural GABA, the low dose applied in the present study had no effect on sleep efficacy or episodes of wakefulness after sleep onset. These findings suggest that a lower dose of GABA is effective in sleep-onset insomnia but not in sleep-maintenance insomnia. In addition, our study demonstrated an increase in slow-wave sleep in patients treated with natural GABA, in line with previous studies.[4-6]

The advantage of using a lower dose (75 mg) of natural GABA is that it has no adverse effects, which might reflect negative side effects being proportional to the dose. Enomoto et al.[7] recently found that the duration of taking prescribed sleeping pills and their first month's dose were correlated with subsequent increases in the dose.

In conclusion, this study suggests that low-dose natural GABA (75 mg) is effective against sleep-onset insomnia, as supported by a decrease in PSG sleep latency without side effects.

Ethics Statement

This study was approved by the Institutional Review Board of Kyung Hee University Hospital at Gandong (IRB No. 2018-11-025). All patients provided written informed consents before random assignment.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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