Original Article

Comparison of the effects of two amino acids, Gamma-aminobutyric acid (GABA) and L-theanine, on sedation, anxiety, and cognition in preoperative surgical patients – A randomized controlled study

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Abstract

Background and Aims: Preoperational anxiety affects the outcome of anesthesia and surgery. Benzodiazepines impair psychomotor performance and cause excessive sedation. L-theanine is a unique amino acid found in green tea. It prevents stress, produces anxiolysis, modulates alpha activity, and provides beneficial effects on mental state, including sleep quality. Gamma-aminobutyric acid (GABA) is a non-proteinogenic amino acid and a phytochemical that is the main inhibitory neurotransmitter in the mammalian brain. It is beneficial in anxiety and stress regulation. Hence, alternative premedicants such as L-theanine and GABA will have a widespread appeal and are safer. The primary objective was to study and compare the effects of L-theanine and GABA on preoperative anxiety, sedation, and cognition in patients posted for major elective surgeries. The secondary objective was to study adverse reactions.

Material and Methods: A total of 168 patients aged between 18 and 55 years, belonging to the American Society of Anesthesiologists physical status class I and II, and satisfying all inclusion criteria were randomly divided into three groups that received either oral L-theanine, oral GABA, or oral alprazolam 0.25 mg. The anxiety score, sedation score, and psychomotor and cognitive performance scores were noted 60 minutes before and after the administration of the drugs.

Results: Alprazolam produced more sedation than GABA and L-theanine ($P = 0.0001$). Psychomotor and cognitive functions improved with L-theanine and GABA ($P = 0.0001$) and decreased with alprazolam ($P = 0.0001$).

Conclusion: GABA and L-theanine result in effective preoperative anxiolysis with minimal sedation and improvement of cognitive skills.

Keywords: Alprazolam, cognition, gamma-aminobutyric acid, L-theanine, preoperative anxiety, sedation

Introduction

Preoperative anxiety is a universal reaction experienced by patients who are posted for surgery. Anxiety can adversely influence the perioperative period.[1] It negatively affects anesthetic and surgical outcomes and recovery. Hence, the use of premedication for preoperative anxiolysis plays an important role.[2] Benzodiazepines are most commonly used to alleviate preoperative anxiety. However, they impair psychomotor performance, cause excessive sedation, and decrease the duration of the rapid eye movement sleep.[3]

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L-theanine is a unique amino acid found in green tea (Camellia sinensis). Green tea is a widely consumed beverage associated with human health. It is a phytochemical that prevents stress, produces anxiolysis, modulates alpha activity, and provides beneficial effects on the mental state, including sleep quality.[4] Gamma-aminobutyric acid (GABA) is a non-proteinogenic amino acid and a phytochemical that is the main inhibitory neurotransmitter in the mammalian brain. It is beneficial in anxiety and stress regulation, circadian rhythm and sleep regulation, memory enhancement, mood, and even perception of pain.[5] This novel study was planned to study and compare the effects of L-theanine and GABA on anxiety, sedation, and cognition in preoperative patients posted for major elective surgeries under general anesthesia.

Material and Methods

This prospective double-blinded randomized controlled study was conducted on patients aged between 18 and 55 years of American Society of Anesthesiologists (ASA) physical status class I and II, posted for elective surgery under general anesthesia at a tertiary health care institute from August 2021 to August 2022 after institutional ethics committee approval (KIMS: ETHCS COMM: 412:2020-21) and getting registered with the Clinical Trials Registry of India (CTRI/2021/08/035694). The study was conducted in accordance with the principles of the Declaration of Helsinki of 1975 as amended in 2013. The patients were randomly allocated into three groups as per a computer-generated list of numbers: Group A (n = 56): Patients received drug P- oral L-theanine 200 mg (NUTRIJA™); Group B (n = 56): Patients received drug Q- oral GABA 500 mg (SOLGAR GABA); and Group C (n = 56): Patients received drug R- oral alprazolam 0.25 mg.

Patients with a blood pressure of <110 mmHg systolic and <60 mm Hg diastolic, mental impairment, those with a history of psychiatric disorders and on antipsychotics, sleep disorders, liver and kidney disorders, and pregnant and lactating women were excluded from the study.

All patients were evaluated a day prior to surgery, and details of the patient were noted. A written informed consent regarding study participation was obtained from the patient. The study drugs were put in similar-looking coded opaque envelopes as per group by the operation theatre (OT) pharmacist who knew the contents of the envelope. The visual analog scale (VAS) for anxiety, Ramsay sedation score, and the objective tests for psychomotor and cognitive performance such as the digit symbol substitution test (DSST) and the trail-making test (TMT) A and B were explained to the patient during that time, and the patient was asked to do it in a sample test the previous evening. The patient was shifted from the ward to the preoperative room 60 minutes before surgery. Baseline oxygen saturation, heart rate, and blood pressure were recorded. The patient was allocated into one of the three groups as per the randomization and was administered the coded envelope by the OT pharmacist/preoperative room nurse, and the patient ingested the drug with a few sips of water in front of the nurse 60 minutes before induction time. Before giving the tablets, the patient's anxiety, orientation, and sedation levels were assessed using VAS anxiety score, orientation score, and sedation score, respectively, by the investigator. The patient was asked to relax and sleep following the intake of the tablet. After 60 minutes, the patient was assessed again with the same parameters as before and the tests were repeated. The study ended at this point. After completion of the study, the drug group code was revealed to the researcher anesthesiologist by the OT pharmacist.

The parameters that were observed included the following: time of administering the drugs, heart rate, oxygen saturation, VAS anxiety score, objective tests for psychomotor and cognitive performance including cognitive and psychomotor function assessed using DSST, and the TMT A and B tests recorded before giving premedication and 60 minutes after premedication.

In a previous study conducted by Lu K *et al.*, it was found that post administration, the mean visual analog mood scale score was 11.37 ± 13.2 in the L-theanine group, whereas it was 17.37 ± 13.2 in the alprazolam arm. In our study, we had three comparison arms; hence, we kept a 1:1:1 ratio of patients in these three arms.[6] Thus, for detecting a true difference in means between the three groups of -7 with a pooled standard deviation of 13.2 units, the study required a minimum sample size of 56 in each group (i.e., a total sample size of 168), assuming equal group sizes, to achieve a power of 80% at 95% confidence interval.

The data were analyzed using the Statistical Package for the Social Sciences (SPSS for Windows, version 22, SPSS Inc., Chicago II USA). Data analysis included univariate and bivariate analysis as per the study objectives. As a first step, normality testing for the data was done using Shapiro–Wilk test. Then, the univariate analysis was done to describe the sociodemographic information and clinical information such as blood pressure, anxiety, cognitive, and sedation scores and their associated side effects before and after administering the drugs. Quantitative variables are presented as mean along with standard deviation [mean ± SD] or median with interquartile range [median (IQR)] depending upon the type of data distribution. Side effects of drugs are presented as numbers and their percentages.

The bivariate analysis was performed in three steps. First, we compared the anxiety, cognitive, and sedation scores and the associated side effects within the three drug groups, that is, pre- and post-comparison within groups A, B, and C. In the second step, the baseline anxiety, cognitive, and sedation scores were compared among the three groups, that is, baseline comparison of group A versus group B, group B versus group C, and group C versus group A. Similar comparisons were done for post-administration data as well. In the third step, we calculated the difference between pre- and post-drug administration scores individually for the three groups for anxiety, cognitive, and sedation scores. The differences among the three groups were then compared statistically.

Independent *t*-test or one-way analysis of variance (ANOVA) was used to compare the group means in the case of continuous data. Independent samples-Wilcoxon signed rank test and independent samples-Median test were used to compare median scores within and between the three groups if the data was either skewed or a discrete numerical. Chi-square test of association was used to compare the side effects of drugs among the three groups. A P value of less than 0.05 was considered significant to reject the null hypothesis.

Results

A total of 168 patients were included in the study [Figure 1]. The distribution of demographic, baseline, and intraoperative variables was comparable between the groups.

The change in values of VAS anxiety scores before and 60–90 minutes after premedication was significant in all three groups as $P < 0.05$ [Table 1 and Figure 2]. Intergroup comparison was done, and a statistically significant difference in VAS anxiety scores was seen when L-theanine was compared with alprazolam and GABA ($P = 0.0001$) and when GABA was compared with L-theanine and alprazolam ($P = 0.0001$) for VAS anxiety scores after giving the premedication. This showed that oral L-theanine, oral GABA, and oral alprazolam were equally effective in producing anxiolysis; the degree of anxiolysis was in the order alprazolam > GABA > L-theanine.

The sedation scores in the two groups, that is, GABA and alprazolam groups, before and after premedication were statistically significant [Table 2 and Figure 3]. They were not significant in the L-theanine group,

The DSST was increased in the alprazolam and GABA groups 60–90 minutes after premedication when compared to before premedication and they were decreased in the alprazolam group [Table 3]. The comparison of the mean difference between the GABA and alprazolam group and the L-theanine and alprazolam group for DSST scores was highly significant, but there was no difference between the GABA and L-theanine group. TMT, including both Part A and B, were significant when before and after premedication scores were compared. During the intergroup comparison, a significant difference was seen when alprazolam was compared to either L-theanine or GABA. There were improvements in TMT scores (both Part A and B) after premedication with L-theanine and GABA. This showed that alprazolam produced the maximum derangement in both psychomotor and cognitive functions after premedication and before surgery. It also showed that it did not produce any psychomotor or cognitive derangement.

Discussion

L-theanine is structurally and chemically similar to L-glutamate. Hence, it has GABA agonist activity and increases brain GABA levels. Studies have demonstrated that L-theanine causes relaxation within 30–40 minutes approximately after ingestion via two mechanisms. First, it directly stimulates the production of α brain waves in occipital, parietal, and frontal brain areas, creating a state of deep relaxation and

Table 1: Comparison of three drugs with VAS scores at 1 h before surgery and 1 h after drug administration by Kruskal one-way analysis of variance (ANOVA)

Drugs	1 h before surgery		1 h after drug administration		Difference		Between 1 h before vs. 1 h after drug administration by Mann–Whitney *U* test		
	Mean	SD	Mean	SD	Mean	SD	% of change	*Z*	*P*
Drug P	2.80	0.40	2.66	0.61	0.14	0.35	5.10	2.5205	0.0117*
Drug Q	2.91	0.44	1.93	0.32	0.98	0.36	33.74	6.2747	0.0001*
Drug R	2.91	0.39	1.13	0.33	1.79	0.46	61.35	6.4515	0.0001*
H	2.3740		111.9450		125.1940				
P	0.3050		0.0001*		0.0001*				
Drug P vs. Drug Q	0.2010		*P*=0.0001*		*P*=0.0001*				
Drug P vs. Drug R	0.1690		*P*=0.0001*		*P*=0.0001*				
Drug Q vs. Drug R	0.9830		*P*=0.0001*		*P*=0.0001*				

**P<0.05 indicates significant. Drug P: Oral L-Theanine 200 mg. Drug Q: Oral GABA 500 mg. Drug R: Oral Alprazolam 0.25 mg. SD: Standard deviation*

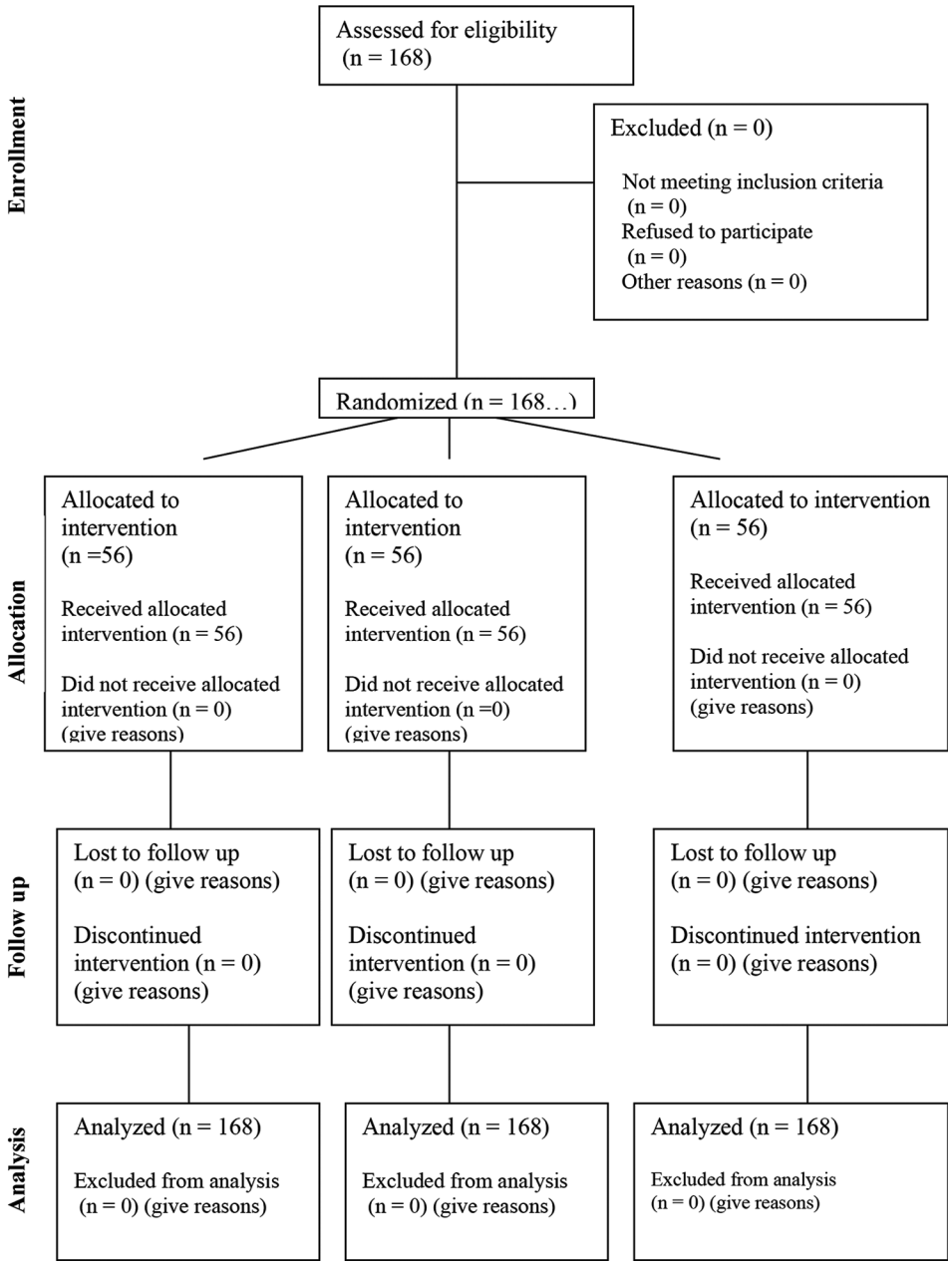

Figure 1: Consolidated standards of reporting trials (CONSORT) diagram

Table 2: Comparison of three drugs (groups P, Q, and R) according to Ramsay sedation scores

Times	Drug P	%	Drug Q	%	Drug R	%	Total	%	χ^2	*P*
1 h before surgery										
Score 0	1	1.79	0	0.00	0	0.00	1	0.60	4.4520	0.3480
Score 1	49	87.50	44	78.57	48	85.71	141	83.93		
Score 2	6	10.71	12	21.43	8	14.29	26	15.48		
1 h after drug administration										
Score 0	1	1.79	0	0.00	0	0.00	1	0.60	125.981	0.0001*
Score 1	47	83.93	2	3.57	0	0.00	49	29.17		
Score 2	8	14.29	54	96.43	56	100.00	118	70.24		
Total	56	100.00	56	100.00	56	100.00	168	100.00		
B/W 1 h before vs. 1 h after drug	Z=1.3416# P=0.1797		Z=6.0308# P=0.0001*		Z=5.6454# P=0.0001*					

**P<0.05 indicates significant, #applied Wilcoxon matched pairs test. Drug P: Oral L-Theanine 200 mg. Drug Q: Oral GABA 500 mg. Drug R: Oral Alprazolam 0.25 mg*

mental alertness similar to that achieved through meditation. The second mechanism is by the formation of the inhibitory neurotransmitter, GABA, which influences the levels of two other neurotransmitters—dopamine and serotonin, which produce relaxation effects.[7] Several human studies have investigated the effects of GABA on stress reduction, sleep enhancement, and other biological activities such as anti-hypertensive, anti-diabetic, anti-cancer, anti-oxidant, anti-inflammatory, anti-microbial, and anti-allergic effects. In the United States, GABA is an ingredient in several dietary supplements. Currently, there is an increasing interest in investigating the effect of GABA-mediated inhibitory

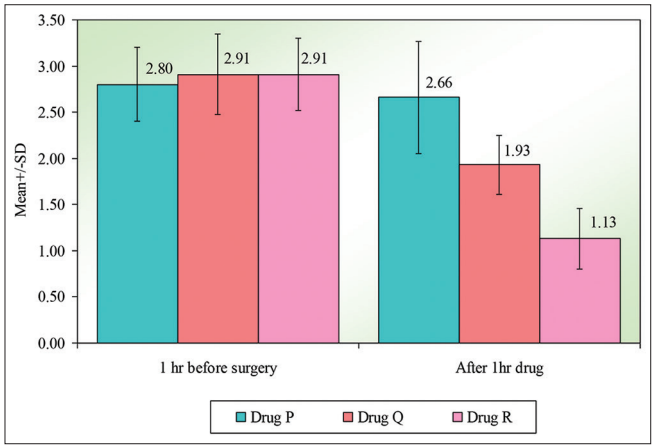

Figure 2: Comparison of three drugs with visual analog scale (VAS) scores for anxiety at 1 h before surgery and 1 h after drug administration. Drug P: Oral L-Theanine 200 mg, Drug Q: Oral GABA 500 mg, Drug R: Oral Alprazolam 0.25 mg, hr: Hour

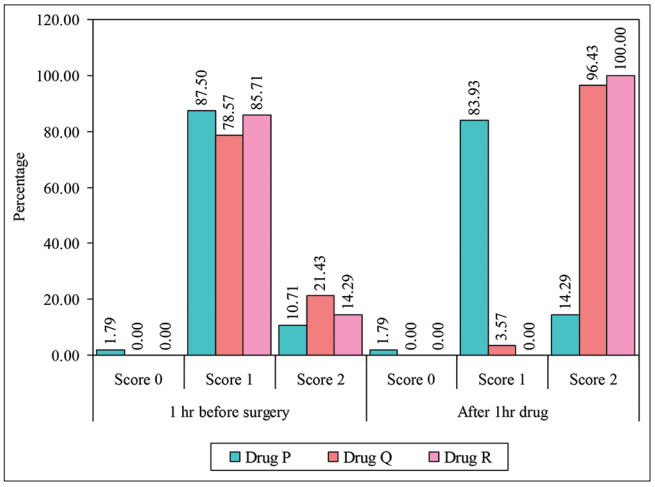

Figure 3: Comparison of three drugs according to Ramsay sedation scores. Drug P: Oral L-Theanine 200 mg, Drug Q: Oral GABA 500 mg, Drug R: Oral Alprazolam 0.25 mg, hr: Hour

Table 3: Comparison of three drugs with mean DSST, TMT A and B scores at 1 h before surgery and 1 h after drug administration by one-way ANOVA

Drugs	1 h before surgery		1 h after drug administration		Difference		Between 1 h before vs. 1 h after drug administration by dependent *t*-test		
	Mean	SD	Mean	SD	Mean	SD	% of change	Paired t	*P*
Drug P	91.77	0.97	94.38	1.66	2.61	1.79	-2.84	-10.926	0.0001*
Drug Q	91.71	1.23	93.91	2.24	2.20	2.25	-2.39	-7.2999	0.0001*
Drug R	91.46	1.24	88.98	2.48	-2.48	2.45	2.71	7.5833	0.0001*
F	1.1060		107.6454		94.1828				
P	0.3333		0.0001*		0.0001*		DSST scores		
Drug P vs. Drug Q	*P*=0.9672		*P*=0.4896		*P*=0.5788				
Drug P vs. Drug R	*P*=0.3444		*P*=0.0001*		*P*=0.0001*				
Drug Q vs. Drug R	*P*=0.4849		*P*=0.0001*		*P*=0.0001*				
Drug P	27.21	2.20	23.45	1.50	3.77	1.91	13.85	14.7868	0.0001*
Drug Q	26.98	2.25	23.91	2.41	3.07	2.10	11.38	10.9639	0.0001*
Drug R	27.36	2.24	30.91	4.19	-3.55	3.30	-12.99	-8.0524	0.0001*
F	0.4040		114.5287		144.8703				
P	0.6683		0.0001*		0.0001*				
Drug P vs. Drug Q	*P*=0.8458		*P*=0.6780		*P*=0.3070				TMT part A
Drug P vs. Drug R	*P*=0.9385		*P*=0.0001*		*P*=0.0001*				
Drug Q vs. Drug R	*P*=0.6463		*P*=0.0001*		*P*=0.0001*				
Drug P	89.70	8.08	84.64	8.66	5.05	5.77	5.63	6.5546	0.0001*
Drug Q	89.52	7.56	84.64	8.80	4.88	6.37	5.45	5.7265	0.0001*
Drug R	90.29	9.43	96.52	9.46	-6.23	6.47	-6.90	-7.2088	0.0001*
F	0.1283		32.6472		60.6733				
P	0.8797		0.0001*		0.0001*				
Drug P vs. Drug Q	*P*=0.9930		*P*=0.9999		*P*=0.9873				TMT part B
Drug P vs. Drug R	*P*=0.9268		*P*=0.0001*		*P*=0.0001*				
Drug Q vs. Drug R	*P*=0.8789		*P*=0.0001*		*P*=0.0001*				

**P<0.05 indicates significant. Drug P: Oral L-Theanine 200 mg. Drug Q: Oral GABA 500 mg. Drug R: Oral Alprazolam 0.25 mg. DSST: Digit symbol substitution test; ANOVA: Analysis of variance; SD: Standard deviation*

neurotransmission, and its potential benefit in counteracting sleep disruption, which can be caused by various conditions, such as stress, diseases, and caffeine intake.[8]

Researchers have used oral L-theanine in doses ranging from 60 mg dual dose to 1200 mg single dose. Haskell *et al*. administered 200 mg of L-theanine, and this stimulated the production of alpha waves in resting participants, causing a sensation of relaxation without drowsiness and side effects.[9] We selected a dose of 200 mg orally because our study group included adult patients and we wanted the maximum effectiveness with the safest maximum dose previously used by other researchers. The peak action of oral alprazolam is from 60 to 90 minutes. Its oral dosage ranges from 0.25 to 1 mg. Alprazolam at doses of 0.5 mg and higher causes impairment in immediate and delayed recall and recognition. Hence, a dose of 0.25 mg was selected for alprazolam. To our knowledge, our study is the first comparative study that compares GABA with L-theanine and alprazolam. Lu *et al*. examined the acute anxiolytic effects of L-theanine with alprazolam, and placebo on behavioral measures of anxiety in healthy human subjects under both relaxed and an experimentally induced anxiety state.[6] The finding of many studies suggests the calming or relaxing effect of L-theanine in the resting state and is consistent. For example, Kobayashi *et al*. showed that L-theanine has greater effects on the generation of alpha activity in a high-anxiety group of patients as compared with a low-anxiety group.[10] Our study showed that oral L-theanine and oral GABA were equally effective in producing anxiolysis when compared with alprazolam. Several studies failed to show the anxiolytic effect of benzodiazepines during experimentally induced anxiety.[3] Kimura *et al*.[11] showed that there are reduced subjective and physiological responses to acute stress following the intake of L-theanine. Lu *et al*. also found that L-theanine can increase alpha wave activity in the parietal and occipital regions of the brain and increase relaxation without increased drowsiness[6]. Ngo and Voto *et al*.[12] showed an increase in cognitive ability in elderly subjects over 55 years of age. Studies have shown that GABA induces relaxation by modulating the sympathetic nervous system.[13] Reduction in stress and relaxation is seen when there are enhanced alpha oscillations, reduced beta activity, and increased alpha/beta ratio on the electroencephalogram. In our study, we found that the sedation scores in all three groups, that is, for alprazolam, L-theanine, and GABA groups, before and after premedication were statistically significant ($P < 0.05$). They were very highly significant in GABA and alprazolam groups. The intergroup comparison of sedation scores showed that alprazolam produced the highest degree of sedation when compared to GABA. L-theanine had no significant effect on sedation. GABA did not produce deep sedation as produced by the alprazolam group. GABA produced adequate sedation, which would induce a natural sleep. It did not induce deep sleep in the patients. Similarly, L-theanine produced calmness and relaxation in the patient without causing excessive sedation. Hence, patients sedated with GABA and L-theanine would require less preoperative monitoring (mild sedation) than patients sedated with alprazolam (moderate to deep sedation).

DSST and TMT are simple and reliable tests for assessing cognitive and psychomotor function.[14] In the current study, the mean difference in DSST scores for before and after premedication comparison in each group (i.e. L-theanine, GABA, and alprazolam) was 2.61, 2.20, and 2.48, respectively [Table 3]. This shows that the DSST scores were increased and the patient performed the test better in GABA and L-theanine group 60–90 minutes after premedication when compared with before premedication. We had familiarized the test the previous evening of the surgery to reduce the practice effect of the tests. Using these tests, we found that alprazolam produced the maximum derangement in both psychomotor and cognitive functions after premedication and before surgery. Furthermore, GABA and L-theanine improved both psychomotor and cognitive function. This profile of oral GABA and L-theanine would add to their advantages because any ideal premedicant would require only the anxiolytic and sedative properties rather than psychomotor or cognitive derangement. Increased theta activity during the eyes-open and reading states supports the findings from the neuropsychological test, showing that L-theanine increases cognitive functions such as memory and attention.[15-17]

The reduction of dysphoric mood and anxiety symptom scores during L-theanine augmentation has been found to be a result of decreased serum brain-derived neurotrophic factor levels. Similarly, improvements in cognitive performance, subject alertness, and complex sensory interactions have also been documented.[18,19] GABA improved or maintained cognitive function in the domains of non-verbal reasoning, working memory, and sustained attention in cognition and in the domains of visuospatial/constructional and delayed memory.[20]

The strength of our study is that it is a randomized double-blind study, and this comparative study is the first study that compares GABA with L-theanine and alprazolam.

The limitations of our study are that no objective assessment of preoperative anxiety was done. We used only subjective measurement of anxiety, that is, VAS. We did not assess the cognitive functions postoperatively at different intervals, which would have provided some light on the usefulness of L-theanine

and GABA for ambulatory or day-care surgeries. Our study group included only adults between 18 and 55 years. Hence, we could not assess the effects of oral L-theanine and GABA in children and the elderly.

Nevertheless, the potential for L-theanine and GABA as premedicants has to be further explored.

Conclusion

Both oral L-theanine and oral GABA decrease anxiety, and GABA produces a greater decrease in anxiety than L-theanine. Oral alprazolam produces a greater decrease in anxiety than oral GABA and oral L-theanine. Oral L-theanine does not produce significant sedation. Oral GABA and oral alprazolam produce significant sedation, and alprazolam produces more sedation than GABA. Psychomotor and cognitive functions improve with L-theanine and GABA, whereas they decrease with alprazolam.

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Conflicts of interest
There are no conflicts of interest.

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