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A Combination of Gamma-Aminobutyric Acid, Glutamic Acid, Calcium, Thiamine, Pyridoxine, and Cyanocobalamin vs Ginger Extract in the Management of Chronic Motion Sickness: A Clinical Evaluation

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ABSTRACT

Background: Motion sickness (kinetosis) is a common and temporarily incapacitant ailment, manageable with behavioral as well as pharmacological measures.
Objective: To assess the effectiveness and safety of a combination of gamma-aminobutyric acid, glutamic acid, calcium, thiamine, pyridoxine, and cyanocobalamin (Group A) (n = 170) and extract of *Zingiber officinale* (ginger) (Group B) (n = 165) in the management of chronic complaints consistent with motion sickness.
Methods: Both groups were tested according to the following end points, under self-paired as well as comparative study designs: reduction of ≥20 score points in the total motion sickness assessment questionnaire (MSAQ) score, percentage of patients presenting a reduction of the total MSAQ score, absolute MSAQ score reduction, physician's assessment scores, final overall assessment of study medication, and willingness to continue treatment. Safety was also evaluated.
Results: There was a statistically significant better performance under both study designs for Group A ($P = 0.05$ using different statistical tests) in all end points. Both regimens were safe, with different neurological and gastrointestinal tolerability outcomes.
Conclusions: Group A and Group B regimens were effective and safe in the management of chronic complaints consistent with motion sickness and the Group A regimen was more effective than Group B.

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Introduction

Motion sickness (kinetosis) is a common collaterality of an afferens mismatch among visual, head/eyes position perception, and body proprioception that commonly occurs in people under slow frequency movements such as during boat travels, elevator dislocation, and car rides. Although it is a benign and spontaneously reversible manifestation in most cases, it is stressful and debilitating for people with chronic complaints consistent with motion sickness as well as for occasionally compromised individuals. Some hypotheses have been forwarded on why visual, head/eyes position perception, and body proprioception incoordination should even manifest itself with nausea and vomiting reflex triggering. Guedry et al[1] propose that this autonomic activation would be expected to drive the motion-sick person away from the phenomenon causing this incoordination in the first place. Whatever the underlying linkage, several nonpharmacologic and pharmacologic resources have been developed and implemented to prevent or reverse motion sickness. The objective of this study was to evaluate the efficacy and safety of a combination of gamma-aminobutyric acid, glutamic acid, dibasic calcium phosphate, thiamine, pyridoxine, and cyanocobalamin vs ginger extract in the management of chronic complaints consistent with motion sickness, under a self-paired and comparative (randomized and double-blind) design.

To maintain body posture and integration between eye and head movements, the central nervous system counts on a so-called velocity storage mechanism, a compensatory system located in the vestibular nuclei of the brain stem that stores activity related to slow-phase eye velocity. The velocity storage mechanism is influenced by vestibular-only neurons (a group of cells that receive afferens from the head, body, and limbs, underpinning the sense of body rotation) that are under the control of the nodulus of the vestibulo-cerebellum. The former sets the time constant of angular vestibulo-ocular reflex (T_{VOR}), a time constant involved in control of eye movements stabilization against rapid angular head movements through angular vestibulo-ocular reflex interaction between visual and vestibular systems and semicircular canals for postural compensation, and interaction between the 3 semicircular canals and the otolith organs (saccule and utricle) of the vestibular apparatus, for the same purpose. It is known that T_{VOR} is directly correlated to motion sickness susceptibility due to asynchronicity among the neurophysiologic elements under its influence (as detailed above), triggered whenever the former is prolonged; one can presume that correcting T_{VOR} could conversely decrease this susceptibility.[2]

Gamma-aminobutyric acid B ($GABA_b$) receptors are located on vestibular-only neurons and their stimulation is associated with low-frequency angular vestibulo-ocular reflex modulation, as well as reduction of both T_{VOR} and velocity storage time. Vestibular-only neurons in their turn can stimulate the velocity storage mechanism, triggering motion sickness, which is experimentally amenable to the inhibitory effects of baclofen, a $GABA_b$ receptor agonist.[3,4] Agonist stimulation of $GABA_b$ could therefore mean that motion sickness is responsive to pharmacologic control through inhibition of vestibular-only neurons.[5] $GABA_b$ synapses on vestibular-plus-saccade neurons are likely to be involved in GABAergic-mediated reduction in motion sickness as well.[2,6]

Vagal nerve impulses transmitted from the gastric lining up to the vomiting center through 5-hydroxytryptamine 3 (5-HT3) (serotonin) afferent neurotransmission, are associated with nausea and vomiting due to gastric disorders in general. Gastric dysrhythmia in their turn, triggered by the presence of food in the stomach in the setting of motion sickness, has been implicated as a secondary mechanism in the pathogenesis of kinetosis nausea.[7,8]

Motion sickness is defined as a set of autonomic symptoms secondary to conflicts between expected vs actual sensory impressions under conditions of motion. Its pathophysiology is based on mismatched inputs among intravestibular structures (semicircular and otolith organs), visual input, kinesthesic proprioceptive system, and velocity storage mechanism.[1,2] There are 3 types of kinetogenic mismatches, a classification based on conflicts among inputs from visual, vestibular, semicircular, and otholit organs: type 1 (conflicting motion-related input from 2 sensory systems), type 2 (when first input signals motion, but the second does not), and type 3 (the opposite).[1]

Motion sickness corresponds to a complex of symptoms ranging from sopite syndrome (early symptoms of incipient motion sickness with apathy and reduced alertness) to severe vomiting, triggered by car travel, sea movement, or plane trips.[1,9] Children, women, and genetically profiled individuals are more susceptible to it.[9] The pathophysiological basis for vomiting during motion sickness is based on neuroanatomic relations among the various structures involved in motion and visceral control in the brain stem. Autonomic reactions like salivation, cold sweating, and vomiting can be triggered via connections between the so-called vomiting center (nucleus tractus solitarius and medullary reticular formation) and either the hypothalamus or the vestibular nuclei.[2]

Motion sickness management is based on the following approaches:[1]

- Behavioral countermeasures
  - Habituation (the most effective intervention, but requires a long-term commitment).
  - Short-term behavioral modifications: changes in body posture (aligning the head with the body, reducing head movements), changes in visual attention (synchronizing the visual system with the motion—focus on the horizon), and reducing intersensory conflict (avoid low-frequency motions and movements outside the axes of motion).
- Pharmacological countermeasures
  - Anticholinergics (scopolamine).
  - Antihistamines (dimenhydrinate and cinnarizine).
  - Sympathomimetics (amphetamine).
  - Antagonists of gastric 5-HT3 receptors (ginger extract).
  - Vestibular nuclei physiology modulators (GABA, glutamate) (proposed in this article).

Materials and Methods

This was a double-blind, comparative, and self-paired, randomized study for efficacy and safety evaluation of 1 plant derivative (160 mg dry rhizome extract of *Zingiber officinale* Roscoe [ginger] corresponding to 8 mg gingerols as coated tablets) vs a combination of GABA tartrate 100 mg, glutamic acid 100 mg, dibasic calcium phosphate 50 mg, thiamine nitrate 25 mg, pyridoxine chloride 10 mg, and cyanocobalamin 5 μg as coated tablets. The primary efficacy end point was percentage of patients presenting a reduction of $\geq$20 score points in the total motion sickness assessment questionnaire (MSAQ) score (see further). Secondary efficacy end points were percentage of patients presenting a reduction of the total MSAQ score, absolute MSAQ score reduction, physician's assessment scores, final overall efficacy assessment of the study medication, and willingness to continue treatment. Safety end points were overall assessment of tolerability and number of patients presenting adverse events. The study design is depicted in Figure 1.

The study population consisted of outpatients of both sexes in the State of Rio de Janeiro, Brazil, from August 2021 to September 2022. The study was performed at Centro Universitário Serra dos Órgãos Medical School. The study protocol and related documents received approval from the ethical committee (approval No.

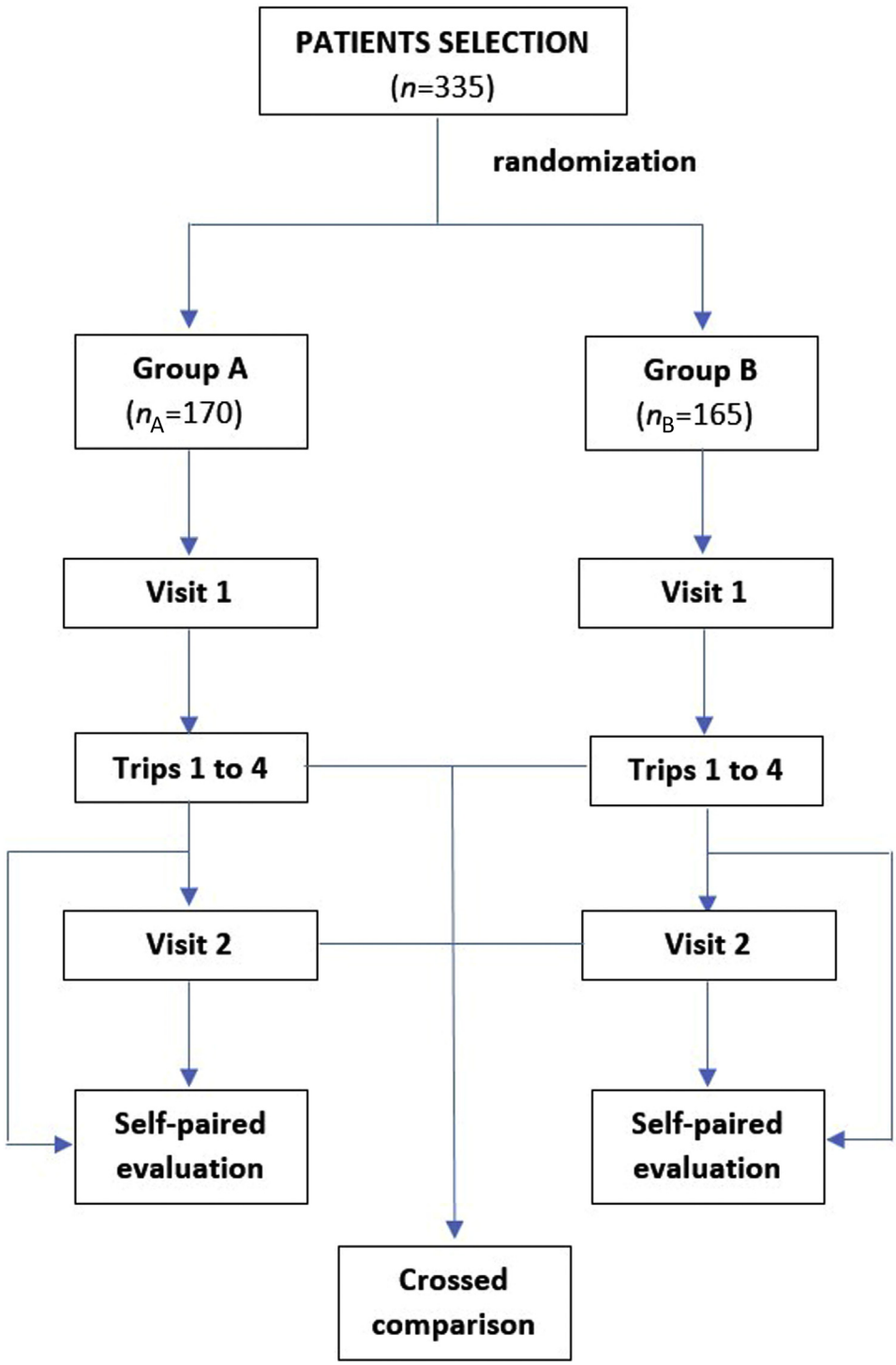

Figure 1. Diagram representing study design of gamma-aminobutyric acid tartrate and combinations (Group A) vs ginger extract (Group B).

4.913.663) before the study startup. The protocol adhered to the World Medical Association's Code of Ethics, specifically the Declaration of Helsinki, for experiments involving humans and is registered at ClinicalTrials.gov (identifier NCT05221892). Patients voluntarily participated in the study. No compensation was given or charges rendered. All patients provided written informed consent before any study-related activity.

Patients were selected according to the following inclusion criteria: individuals of both sexes with ages ranging from 18 and 65 years (reproductive-age women had to practice contraception during the study period), a clinical picture consistent with kinetosis, and signed informed consent. Patients were not eligible if they presented with hypersensitivity to study medications, gallbladder stone history, gastritis history, arterial blood pressure $>145 \times 100$ mm Hg, and concomitant use of other kinetosis medications. All enrolled patients were submitted to a clinical and laboratory screening before the study start.

Motion sickness was assessed using the MSAQ, a 16-item questionnaire for the evaluation of the gastrointestinal, central nervous system, peripheral, and sopite-related manifestations of mo-

tion sickness on a scale of 1 to 9.[10] The lowest possible score per individual is 16 points (no motion sickness symptoms) and the highest possible score is 144 points (worst possible motion sickness symptoms).

All enrolled patients answered the MSAQ form immediately after a ≤15 minutes duration trip (total 4 trips), including type and duration of transportation. Both study medications were administered 15 minutes before Trips 2 to 4 (Trip 1 was exempted). Visit 2 took place after the 4 study trips were completed (within 7 days of Visit 1), and included a scored physician assessment on a 10-point scale rated from 1 (worst evaluation) to 10 (best evaluation), evaluation of willingness to continue treatment on a 10-point scale rated from 1 (least willing) to 10 (most willing to continue treatment), concomitant medication assessment, and final overall efficacy assessment of study medication on a 4-item scale (very good, good, fair, or poor). Adverse event (AE) evaluation was conducted at Visit 2 (posttreatment) and included an overall assessment of tolerability by the patient, nature, duration, and grading of AE (mild, moderate, or severe), serious AE occurrence, treatment interruptions, and continuation of AE at the end of treatment.

Sample size determination was based on the primary end point, calculated to determine the percentage difference in a self-paired sample, and the estimated percentual difference was tested against 0.1 (null hypothesis). This number was based on a previous study of induced motion sickness treated with ginger, in which the maximum percentage MSAQ score difference between treated and untreated was 30%. The difference between the constant and the expected percentual difference was the minimum difference that would be important to detect. The SD of the difference was the function of the SDs before and after treatment and the correlation between them. Considering an average pre- to posttreatment difference of 30% with a 2-tailed alpha of 0.050, an SE of 0.02, and a power of 1.0 (95% CI 0.25–0.35), the sample size of 360 was defined. Taking into account an estimated loss rate of 10% (dropouts, loss of follow-up, and patient withdrawal), the total sample required for this study was 330 evaluable patients.

All data were recorded in the clinical research form. Statistical analysis of collected data was performed using Power and Precision statistical software version 4.1 (Biostat, Englewood, New Jersey). AEs were coded using Medical Dictionary for Regulatory Activities version 21.0 (in Portuguese). Clinical efficacy and safety data were statistically analyzed by comparing the results of Visit 2 relative to Visit 1 and the evolving results of the trips in a self-paired and comparative fashion. Efficacy data were analyzed for the per-protocol population (defined as all patients who completed the study treatment regimen for each treatment trip) and safety data were analyzed for the intent-to-treat population (all participants with at least 1 dose of study medication).

Results

Population profile

A total of 335 patients were included in the study of whom 181 (54.0%) were women and with a mean (SD) age of 43 (11) years. Reported age ranges of motion sickness onset were childhood, adolescence, and adulthood comprising 17, 84, and 234 patients, respectively. One hundred sixty-one patients reported previous treatments as herbal therapies, prescription drugs, over-the-counter, unspecified herbal teas, homeopathy, and combinations under a frequency of 35.2%, 24.4%, 11.1%, 2.0%, 11.8%, and 18.5%, respectively (4 patients reported previous use of ginger extract, and none reported GABA and associations). A number of patients were withdrawn from the study for the following reasons: AE (1 individual), lost to follow-up (3 individuals), concomitant medication (1 individual), protocol violation (2 individuals), and other reasons (1 individual). No significant changes in physical exam results were noted in Visit 2 relative to Visit 1 (Table 1). Details of transportation means and duration of each trip are displayed in Table 2.

Table 1
Physical exam results at Visit 1 (pretreatment) and Visit 2 (end-of-study visit).*

Parameter	Visit 1 (n = 335)	Visit 2 (n = 327)
Weight (kg)	69.9 (13.3)	69.4 (13.0)
Body mass index	24.5 (3.0)	24.3 (3.1)
Heart rate (bpm)	70 (6.8)	69.4 (6.9)
Respiratory rate (ipm)	13.5 (1.7)	13.5 (1.6)
Systolic blood pressure (mm Hg)	120.9 (8.4)	120.4 (8.7)
Diastolic blood pressure (mm Hg)	77 (8.9)	76.5 (8.8)

* Values are presented as mean (SD). No statistically significant difference in relation to Visit 1 ($P > 0.05$ for all parameters [t test]).

Effectiveness and safety

The percentage of patients presenting a reduction of ≥20 score points in the total MSAQ score of Trips 2 through 4 relative to Trip 1 are depicted in Table 3.

There was a statistically significant reduction in the percentage of patients presenting a reduction of ≥20 score points in the total MSAQ score in Group A at Trip 2 (54.1%; $P = 0.05$; 95% CI, 0.45–0.61), Trip 3 (62.3%; $P = 0.05$; 95% CI, 0.55–0.69), and Trip 4 (66.4%; $P = 0.05$; 95% CI, 0.59–0.73) relative to Trip 1. Similarly, there was a statistically significant percentage reduction regarding the same end point in Group B at Trip 2 (43.6%; $P < 0.05$; 95% CI, 0.36–0.51), Trip 3 (50.9%; $P = 0.05$; 95% CI, 0.43–0.59), and Trip 4 (55.1%; $P = 0.05$; 95% CI, 0.47–0.63) relative to Trip 1. Conversely, there was a statistically significant difference in favor of Group A regarding the mean of patients (106 and 82 patients for Groups A and B, respectively) presenting a reduction of ≥20 score points in the total MSAQ score ($P = 0.05$; 95% CI for the mean difference, 21.7–26.2).

The percentage of patients who presented a reduction of the total MSAQ score of Trips 2 through 4 relative to Trip 1 is also depicted in Table 3. There was a statistically significant difference in the percentage of patients presenting a reduction in the total MSAQ score in Group A at Trip 2 (40.0%; $P = 0.05$; 95% CI, 0.33–0.48), Trip 3 (45.2%; $P = 0.05$; 95% CI, 0.38–0.53), and Trip 4 (47.5%; $P = 0.05$; 95% CI, 0.40–0.54) relative to Trip 1.

Similarly, there was a statistically significant percentage reduction regarding the same end point in Group B at Trip 2 (34.4%; $P = 0.05$; 95% CI, 0.27–0.42), Trip 3 (39.6%; $P = 0.05$; 95% CI, 0.32–0.47), and Trip 4 (41.9%; $P = 0.05$; 95% CI, 0.35–0.50) relative to Trip 1. Conversely, there was a statistically significant difference in favor of Group A regarding the mean of patients (164 and 157 patients for Groups A and B, respectively) presenting a reduction in the total MSAQ score ($P = 0.05$; 95% CI for the mean difference, 6.8–7.1). Absolute MSAQ score reduction and score reduction per patient per Trip (both end points Trips 2 through 4) are depicted in Table 4.

There was a statistically significant reduction in the mean absolute MSAQ score in favor of Group A (5339 [369] vs 5992 [374] points for Group B) ($P = 0.05$ t test for 2 independent groups; 95% CI −573 to 732). Similarly, there was a statistically significant reduction in the mean (SD) score per patient per trip in favor of Group A (31.3 [2] vs 36.2 [2] points for Group B) ($P = 0.05$ t test for 2 independent groups; 95% CI, 4.5 to 5.4) (Figure 2). Physician assessment scores for Visits 1 and 2 are depicted in Table 5.

There was a statistically significant increase in physician assessment scores at Visit 2 compared with Visit 1 for both Groups A (1299 points; $P = 0.05$; 95% CI, 0.64–0.77) and B (1124 points; $P = 0.05$; 95% CI, 0.40–0.56). Conversely, there was a statistically

Table 2
Transportation means and duration from Trips 1 through 4.*

Trip parameters	Trip 1		Trip 2		Trip 3		Trip 4	
Types of transportation								
Ferry	97	(28.7)	95	(28.9)	95	(29.1)	93	(28.6)
Car	55	(16.3)	58	(17.6)	58	(17.7)	57	(17.5)
Subway	31	(9.1)	31	(9.4)	31	(9.5)	31	(9.5)
Bus	97	(28.7)	91	(27.7)	92	(28.2)	93	(28.6)
Train	52	(15.4)	49	(14.9)	47	(14.4)	48	(14.7)
Other	5	(1.4)	4	(1.2)	3	(0.9)	3	(0.9)
Total	337	(100)	328	(100)	326	(100)	325	(100)
Trip duration								
15 min	7	(2.0)	4	(1.2)	3	(0.9)	5	(1.5)
20-30 min	83	(24.7)	82	(24.9)	80	(24.5)	74	(22.7)
30 min-1 h	159	(47.4)	155	(47.1)	161	(49.3)	160	(49.2)
≥1 h	86	(25.6)	88	(26.7)	82	(25.1)	86	(26.4)
Total	335	(100)	329	(100)	326	(100)	325	(100)

* Values are presented as n (%).

Table 3
Percentage of patients presenting a reduction of ≥20 score points in the total motion sickness assessment questionnaire (MSAQ) score and percentage of patients presenting a reduction in total MSAQ score.

Studied group	Trip 2	Trip 3	Trip 4
	Percentage of patients presenting a reduction of ≥20 score points in the total MSAQ score		
Group A*	54.1**	62.3**	66.4**
Group B*	43.6**	50.9**	55.1**
	Percentage of patients presenting a reduction of total MSAQ score		
Group A*	40.0**	45.2**	47.5**
Group B*	34.4**	39.6**	41.9**

* $P = 0.05$ (difference between groups; calculated as mean) (1-sample test).
** $P = 0.05$ (relative to trip 1; calculated as percentage) (t test).

Table 4
Absolute motion sickness assessment questionnaire score of Trips 2 through 4 (total score and score per patient per trip).

Studied group	Trip 2		Trip 3		Trip 4	
	Total score*	Score per patient per trip†	Total score	Score per patient per trip	Total score	Score per patient per trip
Group A	5747	33.8	5246	30.8	5026	29.5
Group B	6404	38.8	5903	35.7	5671	34.3

* Mean (SD) for total scores are 5339 (369) points and 5992 (374) points for Groups A and B, respectively.
† Mean (SD) for score per patient per trip are 31.3 (2) points and 36.2 (2) points for Groups A and B, respectively.

Table 5
Physician's assessment (total possible score = 1650).

Studied groups	Visit 1	Visit 2
Group A*	755**	1299**
Group B*	714**	1124**

* $P = 0.05$ (difference between groups calculated as mean) (1-sample test).
** $P = 0.05$ (relative to Visit 1) (t test).

significant difference in favor of Group A compared with Group B (1299 and 1124 points, respectively) ($P = 0.05$; 95% CI, 174–175).

Assessment of willingness to continue treatment end point performed at Visit 2 (1–10 scale) scored mean (SD) 8.2 (2.1) and 6.3 (2.7) for Groups A and B, respectively, with a statistically significant difference in favor of Group A ($P = 0.05$ t test). Results of final overall efficacy assessment of the study medication (performed by the investigator) and overall assessment of tolerability are depicted in Table 6. There is a percentual trend toward a better tolerability profile for both end points in favor of Group A. Results regarding the number of patients presented AEs and their corresponding nature are depicted in Table 7.

Forty-five patients and 77 patients in Groups A and B, respectively, presented AEs (1 event per individual patient). Group B patients seemed to have shown poorer general tolerability, especially regarding gastrointestinal symptomatology. Conversely,

Table 6
Final overall efficacy assessment of the study medication and overall assessment of tolerability.*

Assessment	Group A	Group B
	Final overall efficacy assessment of the study medication	
Very good	72 (43.6)	38 (23.4)
Good	57 (34.5)	52 (31.7)
Acceptable	25 (15.1)	52 (31.7)
Poor	11 (6.6)	20 (12.1)
	Overall assessment of tolerability	
Very good	90 (53.8)	32 (20.2)
Good	47 (27.9)	70 (44.3)
Acceptable	25 (14.8)	35 (22.1)
Poor	5 (2.9)	21 (13.2)

* Values are presented as n (%).

Group B patients reported more frequent neurological complaints. All episodes were mild to moderate in severity, with no serious AEs registered during the treatment period and no dropouts related to safety issues.

Discussion

GABA is a monocarboxylic omega-amino acid and the main inhibitory neurotransmitter in the human central nervous system, whose biochemical precursor is glutamic acid.[11,12] Based on the

Table 7
Number of patients presenting adverse events in each group (most common manifestations between brackets).

Adverse reaction	Group A	Group B
Gastrointestinal	20 events (nausea/vomiting, appetite decrease, diarrhea)	60 events (bloating/flatulence, burning tongue)
Neurological	14 events (sleepiness)	8 events (headache)
Total events	45	77

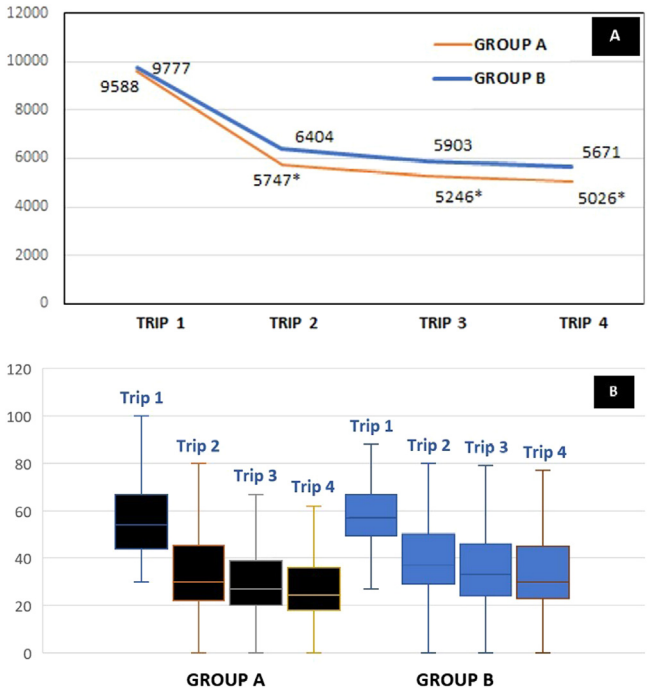

Figure 2. (A) Motion sickness assessment questionnaire (MSAQ) total score per trip (*Statistically significant difference relative to Group B for the same trip) ($P = 0.05$ *t* test for 2 independent groups). (B) Comparative mean MSAQ score per patient per trip.

above description, the rationale of GABA pharmacodynamics, and by extension that of glutamic acid in motion sickness control, can be based on the capacity of the former in stimulating $GABA_b$ receptors in vestibulo-cerebellum system. Pyridoxal-5′-phosphate, the active form of pyridoxine (vitamin B6), is a metabolite involved in the following processes: activation of glutamic-decarboxylase for glutamic acid to GABA conversion, metabolism of specific amino acids (tryptophane, methionine, and cysteine), metabolism of brain amines (serotonin, norepinephrine, and dopamine), and metabolism of fatty acids and phospholipids for neuronal cell membrane.[13,14] Calcium is a mineral neurotransmitter involved in neurotransmitters release modulation through voltage-dependent calcium channels, calmodulin release, and brain vascularity control.[15,16] Thiamine pyrophosphate, the active form of thiamine (vitamin B1), is a coenzyme of the glycolytic pathway of neurons carbohydrates metabolism and its rate of utilization is proportional to that of glucose.[17,18] Cyanocobalamin plays a role in the enzymatic reactions related to the myelin sheath (myelin basic protein amino acids and fatty acids) and axonal tubulins (methionine metabolism) synthetic processes. Vitamin B12 deficiency, a known prevalent disorder, is related to myelinic brain cell edema and demyelination.[19–21] It is plausible that the combination of the above neuropharmacological-acting substances could play a significant role in motion sickness management as adjuvants to GABA and glutamic acid.

Zingiber officinale (ginger) is a Chinese herbal remedy traditionally used to alleviate nausea. Its rhizome is the source of an oleoresin that contains phenolic gingerols, which are rapidly absorbed from the gastrointestinal tract and eliminated through phase II metabolism. Gingerols act as antagonists of gastric 5-HT3 receptors, therefore being potentially useful in the pharmacologic management of nausea in the context of motion sickness. Ginger side effects are minimal.[8,22]

To the best of our knowledge and the available literature, this is the first time the effectiveness and safety of this specific combination of substances (Group A) in motion sickness management have been demonstrated. Both parameters have shown evidence for this combination under a self-paired study design, as well as consolidated through comparison with another medication traditionally used for the same manifestation (ginger). This clinical finding is supported by the pharmacologic action of GABA—and indirectly of its precursor glutamic acid—as $GABA_b$ergic stimulators for motion sickness avoidance, as documented in the literature. Group A combination was generally safe, although it was predictably more frequently associated with neurological side effects, assuming the former acts on the central nervous system. Conversely, ginger was less tolerated in the gastrointestinal tract because it acts on this level of the motion sickness pathophysiological axis. The studied population comprehended participants aged 18 to 65 years, which is a wide age range. Supposedly effectiveness and safety of both tested regimens could have been influenced by this populational aspect. Nonperformance of age subgroup analysis could therefore have represented a limitation of our study.

Conclusions

Both the combination of GABA tartrate, glutamic acid, dibasic calcium phosphate, thiamine, pyridoxine, and cyanocobalamin (Group A) and the dry rhizome extract of *Zingiber officinale* (ginger) (Group B) were effective in the management of chronic complaints consistent with motion sickness, with a statistically superior performance with the Group A combination. Both regimens were well tolerated, with a preponderance for the occurrence of neurological (mostly sleepiness) and gastrointestinal AEs (mostly bloating/flatulence and burning tongue) for the Group A combination and Group B drug, respectively.

Declaration of Competing Interest

This study was cosponsored by Gross Pharmaceuticals (Rio de Janeiro, Brazil) and Centro Universitário Serra dos Órgãos Medical School (Teresópolis, Rio de Janeiro State, Brazil). The authors have indicated that they have no other conflicts of interest regarding the content of this article.

CRediT authorship contribution statement

Carlos P. Nunes: Investigation, Formal analysis. **Claudio Rodrigues:** Investigation, Conceptualization. **Mendel Suchmacher:** Conceptualization, Writing – review & editing. **Claudia Regina Esteves:** Investigation. **Karin Gonçalves:** Validation, Methodology. **Hélio Rzetelna:** Investigation, Data curation. **Rafael V. Rodrigues:** Investigation. **Luciana Regina de Vasconcelos:** Investigation. **Spyros G.E. Mezitis:** Writing – review & editing, Writing –

original draft. **Heros Rabelo:** Methodology. **Renato Kaufmann:** Investigation, Data curation. **Fernanda Schwarz:** Conceptualization, Data curation. **Henrique Goldberg (In Memoriam):** Conceptualization. **Aline Sintoveter:** Writing – review & editing. **Mauro Geller:** Conceptualization, Writing – review & editing.

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