Clinical Evaluation of the Use of Ginger Extract in the Preventive Management of Motion Sickness

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A R T I C L E   I N F O

A B S T R A C T

Background: Motion sickness can be triggered in a variety of situations and is characterized primarily by nausea and vomiting. Ginger is widely used in treating conditions including chemotherapy-associated gastrointestinal symptoms, morning sickness, postoperative nausea, and motion sickness.

Objectives: The primary study objective was to evaluate *Zingiber officinale* extract in the treatment of motion sickness. Secondary objectives were to evaluate treatment effect on Motion Sickness Assessment Questionnaire (MSAQ) score and subscores before and after treatment, and to evaluate treatment tolerability.

Methods: Open-label, single-arm study assessing motion sickness outcomes with and without pre-travel oral treatment with *Zingiber officinale* 160 mg extract (containing 8 mg gingerols). All patients answered the MSAQ on 4 separate occasions following a trip of at least 15 minutes in duration: Trip 1 (pretreatment) and Trips 2, 3, and 4 (after oral treatment with study medication). The primary end point was percentage of patients presenting improvement ≥20 score points on the MSAQ during Trip 2, Trip 3, and Trip 4 in comparison to pretreatment score (Trip 1). Secondary end points included percentage of patients presenting improvement in MSAQ subscores during Trips 2, 3, and 4; percentage of patients presenting treatment-related adverse events; and pre- and posttreatment physician assessment scores.

Results: One hundred eighty-four patients were included and 174 completed treatment. A reduction of ≥20 points in total MSAQ score points occurred in 26.52%, 29.89%, and 29.31% of patients from Trips 2, 3, and 4, respectively. There was no significant difference at Trips 2, 3, and 4 in number of patients presenting improvement ≥20 score points ($P = 0.9579$). There was a significant reduction in total MSAQ scores from Trips 2, 3, and 4 ($P < 0.0001$) compared with Trip 1. Total MSAQ scores did not vary at each trip taken under treatment ($P = 0.28$). There were significant ($P < .001$) improvements in all domain subscores from Trips 2, 3, and 4 in relation to scores from Trip 1. There was a significant improvement in physician assessment scores at Visit 2 ($P < .0001$). Adverse events were reported among 31 patients, mainly affecting the gastrointestinal system. Twenty-four patients (13.04%) reported 39 adverse events considered related to treatment. No significant change in physical exam was noted at Visit 2 in relation to Visit 1.

Conclusions: These open label, historically controlled study results suggest the need for randomized, blinded, placebo and active substance controlled clinical trials. (*Curr Ther Res Clin Exp.* 2020; 81:XXX–XXX)

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Introduction

Motion sickness, also known as kinetosis, is an alteration of the vestibular system in response to a provocative stimulus of movement or perception of movement.[1] The mechanism of action currently proposed is based on conflict or sensory incompatibility between actual and expected vestibular, visual, and kinesthetic patterns. This model is based on the observation that the physical intensity of the stimulus of motion sickness does not necessarily correlate with the degree of intensity of the symptoms.[2]

Motion sickness can be triggered in a variety of situations, including car, train, ship or aircraft travel, amusement park rides, virtual reality, and simulators, as well as in the absence of gravity in space.[2] The incidence of motion sickness varies with the different types of environment that can trigger this condition; however, there is a greater occurrence reported among women and a greater susceptibility in children between ages 6 and 9 years.[3]

Motion sickness is characterized primarily by the hallmark symptom of nausea, in addition to vomiting. Other symptoms related to the clinical picture of motion sickness include stomach awareness, sweating and facial pallor, increased salivation, feeling of body heat, dizziness, and drowsiness—also known as sopite syndrome. There may also be headache, loss of appetite, and an increase in sensitivity to odors.[2,3] The sopite effect of kinetosis is described as a group of symptoms, including apathy, depression, indisposition for work, and decreased participation in group activities. Yawning is a known marker of sopite involvement and is associated with a significant negative effect and reduced performance of tasks.[3,4]

Treatment of motion sickness is divided into 2 categories: behavioral and drug therapy. Behavioral therapy or habituation is often employed by the military and has the advantage of long-term efficacy and freedom from side effects. However, the desensitization process is time-consuming and can require several weeks, and is therefore impractical as a solution for the general population.[5] Drug therapy employs monotherapy or combinations of 3 drug categories: antimuscarinics (eg, scopolamine), H1-antihistamines (eg, dimenhydrinate), and sympathomimetics (eg, amphetamines).[6] Other options used in the management of kinesis include mint, vitamin B-6, and ginger (*Zingiber officinale*).

Z officinale is an herbaceous plant of the family Zingiberacaea and is among the most widely consumed spices worldwide. Other known members of this family include turmeric and cardamom.[7] Ginger is widely used in traditional Chinese and Ayurvedic medicine in the treatment of a variety of conditions, including rheumatism, gingivitis and toothache, asthma, constipation, and diabetes, among others.[8] More recently, in addition to its use in the treatment of motion sickness and although not all indications are supported by robust clinical evidence, ginger has been used in the treatment of nausea and vomiting associated with chemotherapy, morning sickness, postoperative nausea, irritable bowel syndrome, and other gastrointestinal disorders (eg, abdominal cramps, diarrhea, nausea, and bloating).[9,10] Ginger is also used as an herbal treatment for chronic inflammatory diseases, including rheumatoid arthritis, osteoarthritis, and menstrual cramps.[11]

The most commonly used part of the ginger plant is the rhizome, the horizontal stem from which the roots grow. The oleoresin extracted from the ginger rhizome contains bioactive compounds categorized as volatile oils and nonvolatile pungent compounds that include gingerols, shogaols, paradols, and zingerones,[11] with variation in the constituents depending on the geographic origin of the plant and the use of fresh or dried extract.[8] Gingerol is the pungent phenolic compound identified as the main source of the pharmacological and physiological properties attributed to ginger, [6]-gingerol being the bioactive compound found in higher concentrations in studies of oleoresin samples and the most widely investigated in preclinical settings.[11–13] However, gingerols are thermally unstable and at high temperatures undergo transformation into shogaols that confer the pungent and pungent fragrance of ginger and are postulated to be responsible for the pharmacological effects of ginger.[14] The nonpungent substances present in *Z officinale* oleoresin include fats and greases, volatile oils (β-bisabolene, zingiberene, geranial, and neral), carbohydrates, proteins, lipids, vitamin A, vitamin B-3, and minerals.[8]

The metabolism and pharmacokinetics of ginger have not yet been fully elucidated and most of the available studies have been performed in the preclinical environment. However, in a clinical study oral doses of 100 mg to 2 g ginger did not result in detectable levels of the free forms of [6]-, [8]-, and [10]-gingerols or [6]-shogaols, but rather of the respective glucuronides of each compound, which led to the suggestion of rapid absorption after oral ingestion.[15] A recent study correlating in vitro and in vivo results suggested that in the case of ginger phenols the predominant elimination pathway is phase II metabolism.[16]

The proposed mechanisms of action for ginger include interaction with neurotransmitters—specifically as a 5-HT$_3$ receptor antagonist—and with afferent vagal signaling.[17] In mice, [6]-gingerol has been shown to inhibit basal acid secretion, as well as gastric acid secretion when administered together with capsaicin, through the activation of transient receptor potential vanilloid 1.[18] The anti-inflammatory activity of ginger was attributed to inhibition of macrophage and neutrophil activation and modulation of monocyte and leukocyte migration.[19]

This study evaluated the effects of oral therapy with *Z officinale* 160 mg (containing 8 mg gingerols) on motion sickness through the Motion Sickness Assessment Questionnaire (MSAQ). The MSAQ is a validated instrument for multidimensional analysis of motion sickness, consisting of a 16-item questionnaire (rated on a scale of 1–9 points), evaluating the gastrointestinal, central nervous system, peripheral, and sopite symptoms of motion sickness.[20]

Materials and Methods

This was an open, single-arm study including 184 subjects presenting with motion sickness and assessing motion sickness outcomes with and without pretravel oral treatment. The study population consisted of outpatients in the state of Rio de Janeiro, Brazil, from the period of January to March 2019. The study was performed at Centro Universitário Serra dos Órgãos Medical School, and the study protocol and related documents were submitted to and received approval of the ethical committee (approval No. 3.030.118) before study startup. The protocol was conducted in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans and is registered at ClinicalTrials.gov (ID NCT03755596). Patients voluntarily participated in the study. No compensation was given or charges rendered. All patients provided written informed consent before any study-related activity.

The primary objective of this study was to evaluate *Z officinale* 160 mg extract containing 8 mg gingerols (coated tablets containing dry extract *Z officinale* Roscoe rhizome, Gengimin; Farmoquímica, Rio de Janeiro, Brazil) in the treatment of patients presenting motion sickness. The secondary objectives were to evaluate the effect of *Z officinale* extract on the score and subscores of the MSAQ before and after treatment, as well as to evaluate the tolerability of the treatment in the patient population.

Inclusion criteria specified patients between ages 18 and 65 years, clinical presentation of motion sickness, female patients using birth control, and signature of informed consent. Patients with a history of sensitivity to the study medication, gallstones, gastric irritation, hypertension, and in use of other medications for motion sickness were excluded.

The study included 2 visits to the study center: pre- and post-treatment (Visit 1 and Visit 2). Study assessments performed at the study center included medical history and physical examination (height, weight, body mass index, and vital signs), as well as a physician assessment consisting of a 10-point global assessment scale rated from 1 (worst possible evaluation) to 10 points. At pretreatment, patients were queried regarding individual history of motion sickness and previous treatments specific for motion sickness, including herbal, over-the-counter, or prescription medications as well as previous use of ginger and ginger products. At Visit 1 (pretreatment) and Visit 2 (posttreatment), patients were questioned about concomitant use of medications (including any over-the-counter, herbal, or prescription medications for any indication).

Motion sickness was assessed using the MSAQ, a 16-item questionnaire evaluating the gastrointestinal, central nervous system, peripheral, and sopite-related manifestations of motion sickness on a scale of 1 to 9, and scored according to the developer's instructions, by calculating the percentage of total points scored for the overall score, and the percent of points scored within each factor. The lowest possible score is 11.1 points (no influence of motion sickness manifestations) and the highest possible score is 100 points (most severe manifestations).[20]

All enrolled patients were asked to answer the MSAQ on 4 separate occasions, immediately following a trip of at least 15 minutes in duration, and to note the type and duration of transportation used before responding to the questionnaire. The first MSAQ was answered after Trip 1 (no pretravel motion sickness treatment) and subsequent Trips 2, 3, and 4 were completed after travel following oral treatment with study medication. Patients were provided with the study medication (coated tablets containing 160 mg dry rhizome extract of *Z officinale* Roscoe, 8 mg gingerols), to be taken 15 minutes before a trip with a duration of at least 15 minutes.

Visit 2 took place after the four study trips were completed (within 7 days of Visit 1), and included a physical examination, a physician assessment, 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 physician evaluation of overall efficacy and tolerability assessed on a 4-item scale (Very Good, Good, Fair, or Poor). Adverse event (AE) evaluation was conducted at Visit 2 (posttreatment) and included description, start and end dates, severity (mild, moderate, or severe), serious AE occurrence, relation to study drug (as estimated by investigator— probably related, not related, or unknown), whether AE caused interruption of treatment, and continuation of AE at end of treatment.

The primary end point was the percentage of patients presenting improvement ≥20 score points on the MSAQ during Trip 2, Trip 3, and Trip 4 in comparison to pretreatment score (Trip 1). Secondary end points included the percentage of patients presenting improvement in MSAQ subscores (score points) during Trips 2, 3, and 4 in relation to pretreatment scores; the percentage of patients presenting AEs related to the study medication; and pre-and posttreatment physician assessment scores.

Sample size determination was based on the primary end point, calculated to determine the mean difference in a self-paired sample, and the estimated mean (SD) population difference (20 [5.0] points) was tested against 0 (null hypothesis). This number was based on a previous study of induced motion sickness treated with ginger, in which the maximum mean MSAQ score difference between treated and untreated was 20 score points.[21] The difference between the constant and the expected mean difference was the minimum difference that would be important to detect. The standard deviation of the difference was the function of the SDs before and after treatment and the correlation between them. Considering an average pre-/posttreatment difference of 20 (5.0) points with a 2-tailed alpha of 0.050 and a power of 1.0 (95%

CI,19.24–20.77), the sample size of 170 was defined. Taking into account an estimated loss rate of ~8% (dropouts, loss of follow-up, and patient withdrawal), the total sample required for this study was 184 evaluable patients.

All data were recorded in the clinical research form. Statistical analysis of collected data was performed using GraphPad Prism 5 software (San Diego, Calif). Adverse events were coded using Medical Dictionary for Regulatory Activities version 21.0 (in Portuguese) (MedDRA Maintenance and Support Services Organization, McLean, Virginia) and grouped by Preferred Terms. Clinical efficacy and safety data were statistically analyzed by comparison of the results at Visit 2 in relation to pretreatment data. Efficacy data were analyzed for the per-protocol population (defined as all patients who completed study treatment regimen for each treatment trip) and safety data were analyzed for the intent-to-treat population (all subjects with at least 1 dose of study medication). For comparisons of categorical variables, the χ^2 or Fisher test was used, and for continuous variables we used the Student t test or ANOVA. MSAQ scores were calculated and analyzed in accordance with the instructions outlined by the developers of the questionnaire.[20]

Results

A total of 184 patients were included in the study, of which 134 (72.83%) were women and with a mean (SD) age of 36.92 (8.0) years. Age range of onset of motion sickness was in childhood among 37 (20.11%) of the patient population, adolescence among 76 (41.3%), and adulthood in 71 (38.59%). Previous treatment of motion sickness was reported among 132 (71.74%) of the patient population: herbal therapies (37.9%), prescription (28.0%), over the counter (16.7%), unspecified herbal teas (11.4%), homeopathy (3.0%), combination herbal and over the counter (1.5%), combination homeopathy and herbal remedies (0.8%), and behavioral therapy (0.8%). Of patients reporting previous herbal treatment of motion sickness, 2 patients reported previous use of ginger tea.

A total of 10 patients were withdrawn from the study for the following reasons: AE (n = 2), lost to follow-up (n = 2), concomitant medication (n = 2), withdrawn consent (n = 1), protocol violation (n = 1), clinical worsening (n = 1), and clinical worsening and AE (n = 1).

Details of each trip are displayed in Table 1. A reduction of ≥20 score points in the total MSAQ score was observed in 26.52% (48 out of 181), 29.89% (52 out of 174), and 29.31% (51 out of 174) of patients from Trips 2, 3, and 4, respectively, in relation to pretreatment score (Trip 1). There was no statistically significant difference at Trips 2, 3, and 4 in the percentages of patients presenting no change or worsening, improvement <20 points, and improvement ≥20 points ($\chi^2 = 0.65$; df = 4; $P = .9579$) in relation to Trip 1.

Mean (SD) total MSAQ scores from each trip were Trip 1: 40.23 (10.64) (95% CI, 38.77–41.90); Trip 2: 26.46 (12.73) (95% CI, 24.59–28.33); Trip 3: 24.71 (11.65) 95% CI, 22.96–26.45); and Trip 4: 24.64 (12.16) (95% CI, 22.82–26.46) (Fig. 1). Total MSAQ scores did not vary at each trip taken under treatment (Trip 2, Trip 3, and Trip 4: ANOVA; $P = 0.28$). There was a statistically significant reduction in total MSAQ scores at Trip 2 ($t = 17.86$; df = 180; $P < 0.0001$; 95% CI, 12.36–15.40), Trip 3 ($t = 20.19$; df = 173; $P < 0.0001$; 95% CI, 14.0–17.01), and Trip 4 ($t = 20.13$; df = 173; $P < 0.0001$; 95% CI, 14.06–17.09) in relation to the score at Trip 1 (pretreatment). For the per-protocol population, ANOVA of mean total MSAQ scores was significant ($P < 0.0001$) when comparing pre- and posttreatment scores. Using Tukey's multiple comparison test, the mean differences from Trip 1 were 13.78 (95% CI, 10.56–16.99) for Trip 2, 15.53 (95% CI, 12.2–18.77) for Trip 3, and 15.60 (95% CI, 12.35–18.84 for Trip 4).

Additionally, a between-patients repeated measures ANOVA with Tukey multiple comparison and Dunnett multiple comparison tests was performed to compare Trip 1 with Trips 2, 3, and 4 total

Table 1
Type of transportation and duration of travel before and during treatment.

	Trip 1		Trip 2		Trip 3		Trip 4	
	n	%	n	%	n	%	n	%
Type of transportation								
Ferry	52	28.26	50	27.62	47	27.01	47	27.01
Car	22	11.96	22	12.15	20	11.49	20	11.49
Subway	29	15.76	26	14.36	25	14.37	24	13.79
Bus	51	27.72	53	29.28	53	30.46	54	31.03
Train	30	16.30	30	16.57	29	16.67	29	16.67
Total	184	100.00	181	100.00	174	100.00	174	100.00
Trip duration								
15–20 min	5	2.72	5	2.76	5	2.87	5	2.87
20–30 min	43	23.37	43	23.76	43	24.71	45	25.86
30 min–1 h	85	46.20	82	45.30	79	45.40	77	44.25
≥1 h	51	27.72	51	28.18	47	27.01	47	27.01
Total	184	100.00	181	100.00	174	100.00	174	100.00

Table 2
Motion Sickness Assessment Questionnaire (MSAQ) Subscores at Trip 1 (no treatment) and Trips 2, 3, and 4 (following oral treatment).*

MSAQ dimension	Trip 1 (n = 184)	Trip 2 (n = 181)		Trip 3 (n = 174)		Trip 4 (n = 174)	
		Mean	Improvement ≥20 points	Mean	Improvement ≥20 points	Mean	Improvement ≥20 points
Gastrointestinal	46.73	29.62†	65 (35.91)	27.92†	74 (42.53)	27.48†	79 (45.4)
Central	37.39	24.99†	43 (23.76)	23.05†	47 (27.01)	22.97†	53 (30.46)
Peripheral	32.18	22.24†	29 (16.02)	21.01†	37 (21.26)	21.25†	37 (21.26)
Sopite-related	43.61	28.22†	52 (28.73)	26.25†	58 (33.33)	26.48†	64 (36.78)

* Data are means or n (%) for the per-protocol population at each trip.
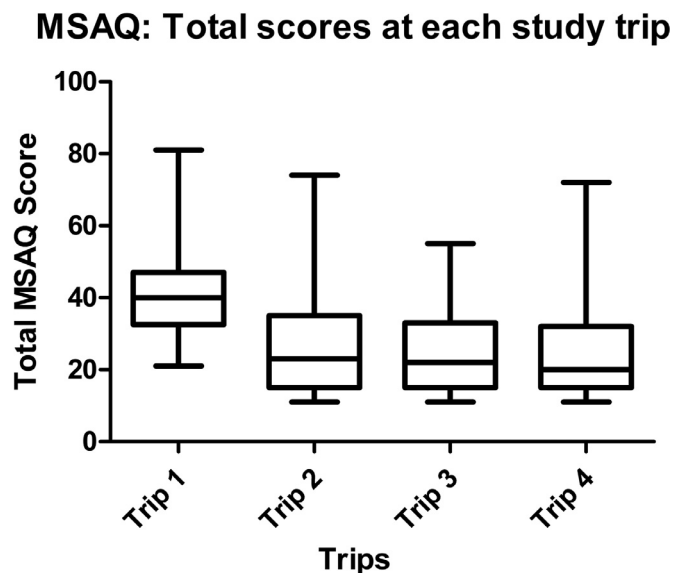† $P < 0.001$ in relation to Trip 1 score on paired Student t test.

Fig. 1. Mean total Motion Sickness Assessment Questionnaire (MSAQ) scores before (Trip 1) and after treatment (Trips 2, 3, 4).

Fig. 2. Physician assessment scores at Visit 1 (pretreatment) and Visit 2 (end-of-study visit).

MSAQ scores (score points) for all patients who were included in the study (intention-to-treat population, using last value carried forward for missing data). In the intention-to-treat population, the significant ($P < 0.0001$) score reductions were confirmed at Trip 2 (mean difference, 13.65; 95% CI, 12.29–15.02), Trip 3 (mean difference, 14.66; 95% CI, 13.3–16.03), and Trip 4 (mean difference, 14.73; 95% CI, 13.36–16.09) in relation to pretreatment scores.

MSAQ subscores for each domain at each trip are displayed in Table 2. There were statistically significant ($P < 0.001$ using Student t test) improvements in all domain subscores from Trips 2, 3, and 4 in relation to scores from Trip 1. There was no variation in domain subscores at each trip taken under treatment ($P = 0.33$
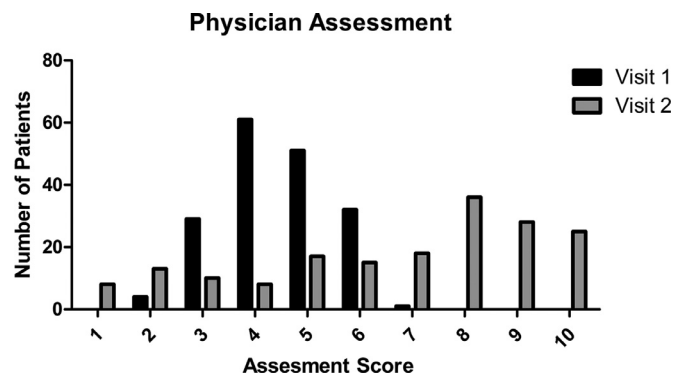
for gastrointestinal items, $P = 0.215$ for central items, $P = 0.453$ for peripheral items; and $P = 0.382$ for sopite-related items using ANOVA). There was no difference in total MSAQ scores or domain scores for the different types of travel during Trips 1, 2, 3, and 4 ($P > 0.05$ for all travel types using ANOVA). On the other hand, total MSAQ scores and domain scores were highest for trips lasting between 30 and 60 minutes (Table 3).

Physician assessment scores are shown in Fig. 2. There was a statistically significant improvement in physician assessment scores at Visit 2 in relation to Visit 1 (pretreatment) ($\chi^2 = 190.1$; df = 9; $P < .0001$).

AEs were reported among 31 patients during the study (Table 4). AE distribution was as follows: 1 AE (n = 13), 2 AEs (n = 11), 3 AEs (n = 6), and 4 AEs (n = 1). Of the total of 57 AEs reported, 17 (29.82%) were mild in severity, 37 (64.91%) were moderate, and 3 (5.26%) were severe. No serious adverse events were registered during the treatment period. Twenty-four patients (13.04%) reported 39 AEs that were considered to be related to the study medication, of which 38 affected the gastrointestinal system: ab-

Table 3

Motion Sickness Assessment Questionnaire (MSAQ) Total and Subscores at Trip 1 (no treatment) and Trips 2, 3, and 4 (following oral treatment) by travel duration.

MSAQ total/ dimension score	Trip duration*				P value†
	15–20 min	21–30 min	31 min–1 h	≥1 h	
Trip 1 (n = 184)					
Total	40.14 (13.12)	36.85 (8.408)	42.04 (11.51)	40.03 (10.11)	0.076
Gastrointestinal	45.00 (11.01)	44.83 (11.53)	47.68 (13.14)	46.95 (11.91)	0.655
Central	36.44 (17.26)	34.26 (10.66)	39.90 (12.02)	35.86 (11.62)	0.054
Peripheral	28.89 (10.92)	28.68 (11.49)	32.64 (13.05)	34.20 (12.54)	0.167
Sopite-related	48.33 (15.16)	38.24 (11.42)	46.14 (15.69)	42.70 (13.40)	0.024
Trip 2 (n = 181)					
Total	15.56 (3.82)	22.50 (11.59)	29.26 (12.91)	26.33 (12.66)	0.007
Gastrointestinal	18.33 (7.24)	25.52 (14.21)	32.55 (15.25)	29.58 (15.11)	0.027
Central	15.11 (4.82)	21.65 (12.44)	27.94 (13.08)	24.05 (12.84)	0.016
Peripheral	14.07 (4.83)	18.35 (7.50)	23.76 (10.18)	23.67 (10.71)	0.004
Sopite-related	14.44 (3.04)	23.64 (13.37)	31.74 (15.73)	27.94 (14.90)	0.005
Trip 3 (n = 174)					
Total	14.86 (2.58)	21.79 (11.59)	26.75 (11.43)	24.91 (11.80)	0.032
Gastrointestinal	17.22 (5.70)	24.03 (13.48)	30.70 (13.81)	28.01 (12.51)	0.017
Central	15.56 (3.51)	20.93 (11.60)	24.92 (11.17)	22.60 (12.07)	0.124
Peripheral	12.59 (2.03)	18.86 (10.09)	21.85 (9.67)	22.30 (9.72)	0.066
Sopite-related	13.33 (1.24)	22.80 (13.45)	28.76 (14.32)	26.65 (14.46)	0.026
Trip 4 (n = 174)					
Total	15.56 (3.82)	21.60 (11.44)	26.91 (12.69)	24.85 (11.60)	0.038
Gastrointestinal	17.78 (6.97)	23.58 (12.82)	30.56 (15.37)	27.42 (12.50)	0.023
Central	15.11 (3.98)	21.09 (12.73)	24.68 (12.75)	22.70 (11.65)	0.209
Peripheral	15.56 (4.83)	18.11 (7.54)	22.70 (10.26)	22.30 (10.14)	0.031
Sopite-related	13.89 (3.40)	22.90 (14.2)	29.22 (15.08)	26.89 (14.59)	0.029

* Values are presented as mean (SD).
† Based on ANOVA.

Table 4

Adverse events reported during treatment by Medical Dictionary for Regulatory Activities (MedDRA Maintenance and Support Services Organization, McLean, Virginia) preferred term (N = 57).

Adverse event	n	%
Abdominal discomfort	1	1.75
Abdominal distension	3	5.26
Akathisia	1	1.75
Anxiety	1	1.75
Asthenia	1	1.75
Decreased appetite	1	1.75
Diarrhea	1	1.75
Dyspepsia	15	26.32
Eructation	15	26.32
Headache	5	8.77
Insomnia	3	5.26
Nausea	4	7.02
Obstipation	2	3.51
Peripheral edema	1	1.75
Somnolence	2	3.51
Vomiting	1	1.75

dominal discomfort (n = 1), abdominal distension (n = 3), diarrhea (n = 1), dyspepsia (n = 13), eructation (n = 15), nausea (n = 4), and vomiting (n = 1). One case of headache was also considered to be related to the study medication. No significant change in physical exam results were noted Visit 2 in relation to those at Visit 1 (Table 5).

In the assessment of willingness to continue treatment performed at Visit 2, 92 patients (51.69%) responded with scores of 8 to 10 points. In the final overall efficacy assessment of the study medication performed by the investigator, the study treatment was considered Very Good for 71 (40.80%) of patients, Good for 39 (22.41%), Acceptable among 34 patients (19.54%), and Poor in 30 patients (17.24%). Overall assessment of tolerability of the study medication was considered Very Good in 78 (44.83%) patients, Good in 60 (34.48%) patients, Acceptable for 29 (16.67%) patients, and Poor among 7 patients (4.02%).

Discussion

A search of the available literature was performed in the following online databases: PubMed, Google Scholar, Scopus, Lilacs, and Cochrane Library, using search terms *Ginger*, *Motion Sickness*, *MSAQ*, and *Motion Sickness Assessment Questionnaire* (English/Portuguese languages, no date limits) indicated that this is the first clinical study evaluating the effect of ginger extract on motion sickness using the MSAQ for land-based travel. A previous study evaluated the effect of ginger on air sickness using the MSAQ, and reported lower overall MSAQ scores and subscale scores among patients prophylactically treated with 1 g ginger root powder before exposure to provocative stimulus in the Barany chair.[21] The results of our study indicate that pretravel treatment with ginger extract could be helpful to patients who are required to use ground transportation methods on a more day-to-day basis, such those utilized during the study treatment period (ie, car, bus, train, ferry, and subway).

MSAQ was selected as an assessment tool in this study because it evaluated motion sickness as a multidimensional construct, providing scores for the different dimensions of motion sickness and also an overall score.[20] The MSAQ includes an evaluation of the sopite symptoms associated with motion sickness that are absent in other commonly employed motion sickness evaluation tools such as the Pensacola Diagnostic Index and the Pensacola Motion Sickness Questionnaire.[20]

The higher incidence of female patients in our study population is in keeping with the literature reporting an increased rate of incidence and severity of motion sickness among women.[2] The higher pretreatment MSAQ subscores in the Gastrointestinal Items domain compared with the remaining domains observed in the present study are also in accordance with the literature, where the primary signs and symptoms of motion sickness are described as nausea and vomiting.[2,3]

In the analysis of the primary end point, there was improvement of ≥20 points on the MSAQ total score for all trips taken while under treatment in relation to the pretreatment score, and these improvements were observed in ≥25% of patients at

Table 5
Physical exam results at Visit 1 (pretreatment) and Visit 2 (end-of-study visit).

Parameter	Visit 1 (n = 184)		Visit 2 (n = 174)		Change from pretreatment P value from t test
	Mean	SD	Mean	SD	
Weight (kg)	66.53	12.44	66.15	12.26	.347
Body mass index (kg/cm^2)	24.26	3.022	24.17	2.98	.440
Heart rate (bpm)	69.95	6.994	69.28	7.07	.151
Respiratory rate (ipm)	14.71	1.884	14.70	1.77	.851
Systolic blood pressure (mmHg)	119.9	8.475	119.6	8.40	.473
Diastolic blood pressure (mm Hg)	76.18	10.01	75.52	10.55	.053

each trip, along with statistically significant improvements in total MSAQ scores and domain subscores at each trip during the treatment period. The homogeneity of the total MSAQ scores and subscores from Trips 2, 3, and 4 indicate reproducibility of the results and a consistent effect of the treatment on the signs and symptoms of motion sickness in the treated population.

Use of *Z officinale* extract in the treatment of nausea has been previously investigated in clinical studies of postoperative nausea and motion sickness. In the prophylaxis of kinetosis, 1 study evaluated 203 volunteers treated with 250 mg *Z officinale* extract for the prevention of sea sickness and compared the action of this extract with that of cinnarizine, cyclizine, dimenhydrate, meclizine, and hyoscine, reporting a comparable efficacy ginger extract with these substances when ingested 2 hours before travel (no motion sickness in 78.3% of the *Z officinale* treated population).[22] Oral administration of 1 g *Z officinale* extract significantly reduced postoperative nausea in women undergoing laparoscopic gynecological surgery compared with placebo and significantly reduced the need for postoperative antiemetic use in the population treated with the ginger extract.[23] In the treatment of pediatric motion sickness, the use of *Z officinale* at the daily dose of 1.25 g was superior to the use of metoclopramide 25.17 mg/d in the prevention of vomiting.[10]

Ginger extract was also shown to be effective in clinical studies of induced motion sickness and demonstrated superiority in vertigo reduction compared with placebo using an oral dose of 1 g powdered ginger root.[24] Mowrey and Clayson[25] used a rotating chair to induce motion sickness and demonstrated the superiority of encapsulated powdered ginger root extract 1.88 g compared with dimenhydrinate and placebo in reducing the symptoms of motion sickness. A subsequent study reported little prophylactic effect of pretreatment with powdered ginger 500 mg on circular motion-induced nausea, but inhibition of tachygastria was identified.[26] Lien et al[27] reported that oral doses of 1 g and 2 g encapsulated ginger effectively reduced nausea, tachygastric activity, and the release of vasopressin induced by circular vectors.

The study treatment was generally well tolerated, with no reports of serious adverse events during the study period and no change in physical exam parameters assessed pre- and posttreatment. The majority of the adverse events occurring during the treatment period were also related to the gastrointestinal tract. Oral use of ginger has been associated with mild gastrointestinal side effects, including pyrosis and eructation,[9,28,29,30] both of which were observed during the treatment period in the current study population. Two patients reported somnolence during the treatment period. This side effect, although present in the current patient population, was considerably lower compared with the incidence reported with use of other antimotion sickness medications such as antihistamines and dimenhydrate. In a study comparing the use of ginger and dimenhydrinate in the treatment of nausea and vomiting among pregnant women, Pongrojpaw et al[31] reported a significantly lower incidence of drowsiness among the patients treated with ginger (5.88% vs 77.64%).

Study limitations and weaknesses include the design that was limited to an open, single-arm comparison of pre- and post-

treatment results. Prior use of ginger and ginger products by the patient was questioned at pretreatment as part of previous motion sickness treatment, but was not investigated separately from other previous treatments. Future studies of ginger in motion sickness should use a primary end point other than that selected for the present study, such as mean MSAQ scores. The use of percentage of patients with improvement ≥20 points on the MSAQ as primary end point was limited because it did not allow for evaluation of extent of improvement. Furthermore, selection of PP population for the analysis of efficacy may lead to bias, so we also suggest including an analysis of the ITT population in the design of future studies.

Additionally, we did not include specific questions about prior experience with the study drug, or use of ginger or ginger products by members of the patient's family. This could represent an unexplored source of information or bias, because prior family use could influence a patient's belief in efficacy of ginger as a treatment for motion sickness. Another potential source of bias that was not addressed in the study design was the investigators' prior experience and opinion as to effectiveness of ginger for motion sickness treatment. As an open-label design, we acknowledge the possibility of a placebo effect on account of patient and prescriber beliefs.

Although the study design was limited to a single-arm, open design, the data obtained suggest confirmation of the hypothesis that oral administration of *Z officinale* 160 mg (8 mg gingerols) would result in improvement of the treated participant's motion sickness, demonstrated by the MSAQ scores and differences observed between trips taken before and after treatment. In the design of future double-blind, randomized controlled trials to confirm these findings, investigators should take into account the characteristic odor of ginger, which may be present despite the coated tablet formulation used in the present study. Future studies should also take into account family history of motion sickness to investigate a possible influence of this factor on treatment outcomes.

Conclusions

These open label, historically controlled study results suggest the need for randomized, blinded, placebo and active substance controlled clinical trials.

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Declaration of Competing Interest

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