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Efficacy of ginger as antiemetic in children with acute gastroenteritis: a randomised controlled trial

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Summary

Background: Ginger is a spice with a long history of use as a traditional remedy for nausea and vomiting. No data on the efficacy of ginger are presently available for children with vomiting associated with acute gastroenteritis (AGE).

Aim: To test whether ginger can reduce vomiting in children with AGE.

Methods: Double-blind, randomised placebo-controlled trial in outpatients aged 1 to 10 years with AGE-associated vomiting randomised to ginger or placebo. The primary outcome was the occurrence of ≥1 episode of vomiting after the first dose of treatment. Severity of vomiting and safety were also assessed.

Results: Seventy-five children were randomised to the ginger arm and 75 to the placebo arm. Five children in the ginger arm and 4 in the placebo arm refused to participate in the study shortly after randomisation, leaving 70 children in the ginger arm and 71 in the placebo arm (N = 141). At intention-to-treat analysis (N = 150), assuming that all children lost to follow-up had reached the primary outcome, the incidence of the main outcome was 67% (95% CI 56 to 77) in the ginger group and 87% (95% CI 79 to 94) in the placebo group, corresponding to the absolute risk reduction for the ginger versus the placebo group of −20% (95% CI −33% to −7%, $P = 0.003$), with a number needed to treat of 5 (95% CI 3 to 15).

Conclusion: Oral administration of ginger is effective and safe at improving vomiting in children with AGE.

Trial registration: The trial was registered on https://clinicaltrials.gov/ with the identifier NCT02701491.

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1 | INTRODUCTION

Vomiting is a common symptom in childhood and has many causes, ranging from self-limited to life-threatening conditions.[1] Vomiting is the presenting symptom in up to 75% of children with acute gastroenteritis (AGE), where it contributes to fluid loss, failure of oral rehydration therapy, and emergency admission to the hospital.[2,3] Nearly 80% of Italian pediatricians prescribe antiemetic drugs to children with AGE, mostly off-label.[4-6] The antiemetic drugs most frequently prescribed in Europe and Italy are domperidone, a dopamine receptor antagonist, and ondansetron, a $5-HT_3$ antagonist.[6] Current evidence shows that ondansetron but not domperidone is effective for the treatment of AGE-associated vomiting in the emergency setting.[2,7]

Ginger (*Zingiber officinale*) is a spice with a long history of use as traditional remedy for nausea and vomiting.[8] The active phenolic compounds of ginger, that is, gingerols, zingiberene and shogaols, have also anti-inflammatory and anti-oxidant properties. The antiemetic action of ginger has been investigated in various conditions including motion sickness, pregnancy, post-anesthesia, post-surgery, and chemotherapy-induced nausea and vomiting.[9-25] Given at doses up to 2 g/day, ginger is effective at controlling vomiting without side effects. Besides its general anti-inflammatory action,[26,27] potential mechanisms of action of ginger include the inhibition of $5-HT_3$ and muscarinic acetylcholine (M3) receptors, and the modulation of esophageal and gastrointestinal motility.[17,26,28]

The pharmacological properties of ginger have been investigated mostly in adults, and no data are available on its effects in children. However, many ginger-based food supplements are increasingly available on the market and are used for the prevention and treatment of vomiting in children without any proof of efficacy. Therefore, the present randomised trial was designed to test whether ginger can reduce AGE-associated vomiting in children.

2 | METHODS

2.1 | Trial design

This randomised, double-blind, parallel-arm, placebo-controlled trial was performed in collaboration with family pediatricians of the Naples city area working for the Italian National Health System and was coordinated by the Department of Translational Medical Science of the University Federico II. The trial was approved by the Ethics Committee of University Federico II of Naples and was performed in accordance with the Helsinki Declaration (Tokyo revision, 2004), and with the pertinent European and Italian regulations about privacy. Written informed consent to participate in the study was obtained by the parents of the children. The trial was registered on https://clinicaltrials.gov/ with the identifier NCT02701491. Such registration was performed before the enrollment of the first patient.

2.2 | Participants

The inclusion criteria were age between 1 and 10 years; suspected AGE-related symptoms lasting <12 h: AGE-associated vomiting (not bilious or bloody) from <4 h; modification of stool pattern lasting <12 h; mild to moderate dehydration evaluated as described elsewhere.[29]

The exclusion criteria were concomitant presence of other diseases, including neurologic and neuropsychiatric diseases; genetic and metabolic diseases, autoimmune diseases, immunodeficiencies, celiac disease, cancer, adverse food reactions (including ginger allergy); functional gastrointestinal disorders; inflammatory bowel diseases; liver diseases; pancreatic diseases; malformations of the gastrointestinal tract; infectious diseases other than AGE; severe dehydration; malnutrition defined as weight-for-height <3 standard deviation scores (SDS); previous surgery of the respiratory, gastrointestinal or urinary tract; use of gastric acidity inhibitors, antibiotics, antiemetics or other drugs in the 2 weeks before the enrollment; use of prebiotics, probiotics or symbiotics in the 2 weeks before the enrollment; participation to other studies.

We evaluated socioeconomic status according to the Hollingshead Four Factor Index for Socioeconomic Status, which is a validated tool to assess this variable.[30]

The final diagnosis of AGE was reached in the presence of ≥3 bowel movements of soft or liquid stools over 24 h, with or without fever, following the guidelines of the European Society for Pediatric Gastroenterology Hepatology and Nutrition and of the European Society for Pediatric Infectious Diseases. [31] Microbiological and other laboratory investigations were performed only for specific clinical reasons.

2.3 | Intervention

The placebo and ginger products were in liquid form and their composition is given in Table 1. Products were produced under Good Manufacturing Practice by the Laboratory of Budetta Farma (Montecorvino Pugliano, Italy). Only a single batch of both ginger and placebo were used in the whole study. The distribution of the treatments was carried out by the coordinator center (Department of Translational Medical Science at the University Federico II, Naples, Italy). The packaging, color, weight, smell and taste of the ginger and placebo were similar. The similar smell and taste were obtained by adding anise and aromas to both products. The first dose of treatment (20 drops containing 10 mg of product) was administered by the family pediatricians immediately after the enrollment of the children and was followed by the administration of hypotonic oral rehydration solution (ORS) after 30 min.[31] The parents were instructed to administer 20 additional drops of treatment every 8 h after the first dose, until the resolution of vomiting. Additional doses were provided only in the presence of ≥1 episode of vomiting in the previous 8 h. The parents received a glass bottle with a pipette and a recyclable cardboard case and were instructed by their family pediatricians on how to use it. In addition, the

TABLE 1 Composition of ginger and placebo

	Placebo (% of weight)	Ginger (% of weight)
Water	48.37	47.37
Fructose	40	40
Sodium citrate	5	5
Anise	0.02	0.02
Vitamin B1	0.03667	0.03667
Vitamin B6	0.04665	0.04665
Vitamin B2	0.04668	0.04668
L-alanine	0.25	0.25
Potassium citrate	4.25	4.25
Citric acid	1.75	1.75
Aroma	0.18	0.18
Potassium sorbate	0.03	0.03
Stevia Rebaudiana	0.02	0.02
Zingiber officinale hydroglycerin extract	—	1
Total	100	100

Note: 20 drops dose contained 10 mg of ginger.

parents were given a daily diary and were instructed by the family pediatricians on how to compile it. The diary recorded: quantity of ORS; whether ORS was refused; number of episodes of vomiting; presence of diarrhea or abdominal pain; number of bowel movements; stool consistency (Bristol stool scale); presence of systemic symptoms such as fever, headache, and irritability; suspected adverse reactions; hospitalisations; use of intravenous fluid therapy; number of days of school lost by the children; number of days of work lost by the parents. A complete medical examination was performed every 24 h by the family pediatricians until the disappearance of all AGE-related symptoms. Unscheduled visits were performed if necessary.

2.4 | Outcomes

The primary outcome was the occurrence of ≥1 episode of vomiting after the first dose of ginger or placebo administered by the family pediatricians. The secondary outcomes were the incidence and the number of episodes of vomiting 24 h (day 1) and 48 h (day 2) after the first dose of treatment. Other outcomes were the quantity of ORS taken by the children in the 4 h after the first dose of treatment; the number of children refusing ORS; the number of children with diarrhea at 24 h (day 1), 48 h (day 2) and 72 h (day 3) from the first dose of treatment; the number of children requiring intravenous fluid rehydratation; the number of children requiring hospitalisation; the number of children not attending school at 24 h (day 1), 48 h (day 2) and 72 h (day 3) from the first dose of treatment.

2.5 | Sample size calculation

Seventy-three subjects per arm were needed to detect an absolute difference of 20% (from 35% to 15%) in the occurrence of ≥1 episode of vomiting after the first dose of treatment between the placebo arm and the ginger at an alpha level of 0.05 with a power of 0.80 (Pearson's chi-squared test) (Stata 14.0, Stata Corp, College Station, TX, US). Such difference was considered clinically relevant in another study.[29] Estimating a dropout rate <3% basing on the results of a previous study,[29] we enrolled 75 subjects per arm, for a total of 150 subjects.

2.6 | Randomisation

The family pediatricians administered the treatment according to a computer-generated stratified randomisation list produced using the *ralloc* command[32] (Stata 14.0, Stata Corp, College Station, TX, USA). The randomisation list employed 5 strata, 1 for each family pediatrician involved into the study, and block sizes of 2. Thus, each pediatrician had her/his own randomisation list involving 30 children randomly assigned to ginger or placebo in 1:1 ratio using block sizes of 2.

2.7 | Allocation concealment

Ginger and placebo were packaged in glass bottles and consecutively numbered according to the randomisation list generated for each family pediatrician (see Section 2.6.).

2.8 | Blinding

The family pediatricians (assessors of the primary outcome), the children and their parents (assessors of the secondary and other outcomes), and the researchers who performed data entry, were blinded to the treatment. The statistician who performed the analysis was not blinded to the treatment.

2.9 | Data collection

Study monitoring was performed by an independent clinical trial monitor and included on-site visits and telephone interviews with family pediatricians. The clinical trial monitor reviewed the clinical forms for completeness, clarity, and consistency. All the data were recorded anonymously and entered into the study database by the same researcher. The study database underwent data cleaning according to standard procedures and was locked before statistical analysis.

2.10 | Compliance

To assess compliance to the treatment, the parents were asked to return the bottles containing the treatment. Compliance to the treatment was defined as the consumption of 100% of it.

2.11 | Statistical analysis

Most continuous variables had non-Gaussian distributions, and all are reported as medians and interquartile ranges (IQR). Discrete variables are reported as numbers and proportions. The SDS of weight, height, and body mass index (BMI) were calculated using the World Health Organisation reference data.[33]

The primary outcome, that is, the occurrence of ≥1 episode of vomiting after the first dose of treatment, was evaluated using a binomial regression model. The response variable of the model was the occurrence of ≥1 episode of vomiting after the first dose of treatment (discrete: 0 = no; 1 = yes) and the predictor variable was treatment (discrete: 0 = placebo; 1 = ginger). The point estimate and the 95% confidence interval (95% CI) of the absolute risk reduction (ARR) were obtained from the model.[34] The 95% CI of the number needed to treat (NNT), that is, the number of patients to treat to prevent the occurrence of ≥1 episode of vomiting after the first dose of treatment, was calculated using Bender's formula.[35] We performed an intention-to-treat analysis (ITT) of the primary outcome by considering the children lost after randomisation as follows: (1) all missing values of the primary outcome set to the worst outcome in both the ginger and placebo arms (equal-case scenario ITT) and (2) missing values of the primary outcome set to the worst outcome in the ginger arm and to the best outcome in the placebo arm (worst-case scenario ITT).[36] The worst outcome was defined as the occurrence of ≥1 episode of vomiting after the first dose of treatment; the best outcome was its opposite. The equal-case scenario ITT for the primary outcome was prespecified by the study protocol, as per standard practice. The worst-case scenario ITT for the primary outcome was implemented post hoc.

The secondary outcomes, which involve repeated measures, were evaluated using per-protocol analysis. The incidence rate of vomiting after 24 h (day 1) and 48 h (day 2) from the first dose of treatment was evaluated using a binomial regression model for repeated measures.[34,37] The response variable of the model was the incidence of vomiting (discrete: 0 = no; 1 = yes), and the predictors were treatment (discrete: 0 = placebo; 1 = ginger), time (discrete: 0 = day 1; 1 = day 2), and a treatment × time (discrete × discrete) interaction. Repeated measures were taken into account by using subject-specific cluster confidence intervals. Two prespecified between-group (ginger vs. placebo) within-day (day 1 and day 2) contrasts were used to calculate the time-specific ARR. ARR and p values were corrected using a Bonferroni correction for two contrasts (day 1 and day 2).

The number of episodes of vomiting were calculated using a negative binomial regression model for repeated measures.[34,37]

The response variable of the model was the number of episodes of vomiting (count) and the predictors were treatment (discrete: 0 = placebo; 1 = ginger), time (discrete: 0 = day 1; 1 = day 2), and a treatment × time (discrete × discrete) interaction. Repeated measures were taken into account by using subject-specific cluster confidence intervals. Two prespecified between-group (ginger vs. placebo) within-day (day1 and day 2) contrasts were used to calculate the time-specific ARR. ARR and P values were corrected using a Bonferroni correction for two contrasts (day 1 and day 2).

The remaining outcomes were reported only as descriptive (and not inferential) statistics, using medians and interquartile ranges (IQR) for continuous variables and numbers and proportions for discrete variables. Such outcomes were: quantity of ORS assumed by the children in the 4 h after the first dose of treatment; number of children refusing ORS; number of children with diarrhea after 24 h, 48 h and 72 h from the first dose of treatment; number of children requiring intravenous fluid therapy; number of children requiring hospitalization; number of children not attending school after 24 h, 48 h and 72 h from the first dose of treatment.

Statistical analysis was performed using Stata 16.1 (Stata Corporation, College Station, TX, USA).

3 | RESULTS

3.1 | Flow diagram

The trial was performed between March 2016 and April 2017. The flow diagram of the trial is depicted in Figure 1. A total of 168 children were assessed for eligibility and 18 were excluded, 11 because they did not meet the inclusion criteria, and 7 because their parents declined to participate in the study. The remaining 150 children were randomised in a 1:1 ratio to ginger (n = 75) and to placebo (n = 75). Five children in the ginger arm and 4 in the placebo arm abandoned the study shortly after randomisation, leaving 70 children in the ginger arm and 71 children in the placebo arm.

3.2 | Baseline data

Table 2 shows that the children randomised to placebo and ginger had similar baseline features. All children were from families of middle socioeconomic status and lived in the city area of Naples. The vaccination status was similar in the two groups and no child had received anti-Rotavirus or anti-Influenza vaccination (data not shown).

3.3 | Primary outcome

The primary outcome, that is, the occurrence of ≥1 episode of vomiting after the first dose of treatment, is reported in Table 3.

Assuming under ITT that all children lost to follow-up had reached the primary outcome, the ARR was −20% (−33% to −7%, P = 0.003,

FIGURE 1 Flow of the children through the study
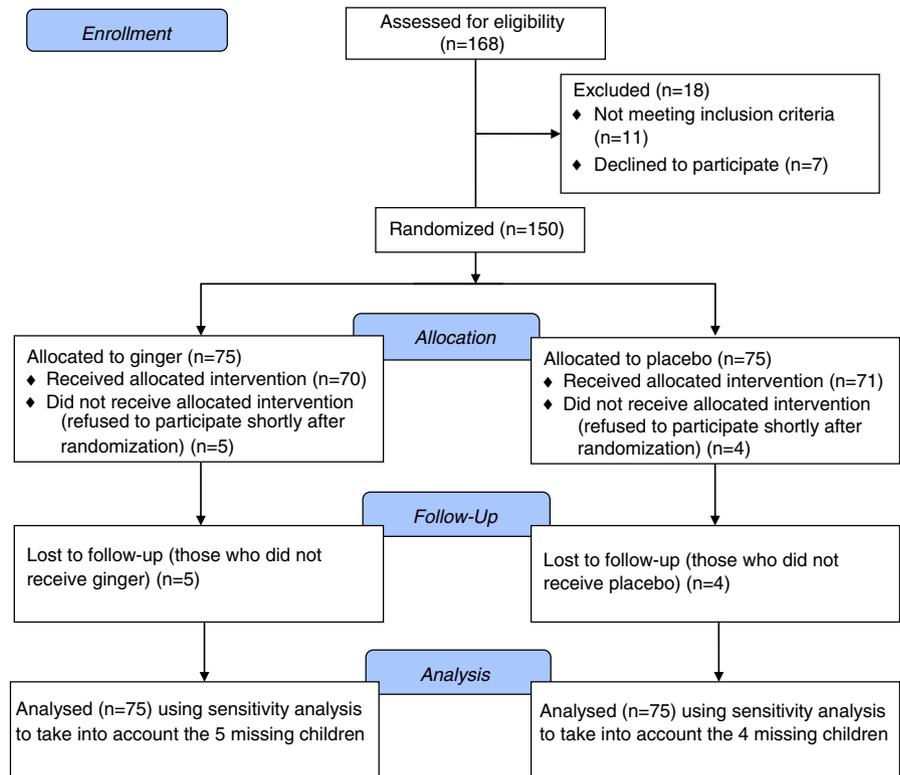
N = 150). Under the worst-case scenario ITT analysis, that is, assuming that the 4 children lost in the placebo arm had not vomiting and the 5 children lost in the ginger arm had vomiting, the ARR was −0.15 (95% CI −0.29 to −0.006, P = 0. 038, N = 150) for ginger versus placebo. Ignoring children lost to follow-up, that is, performing a per-protocol analysis, the ARR was −22% (−35% to −8%, P = 0.002, N = 141).

3.4 | Secondary outcomes

Table 4 gives the incidence of vomiting at 24 h and 48 h from the first dose of treatment (per-protocol analysis, binomial regression). The ARR in the incidence of vomiting for the ginger versus the placebo arm was −22% (P = 0.005) at day 1 and −19% (P = 0.04) at day 2.

Table 5 gives the number of episodes of vomiting at 24 h and 48 h after the first dose of treatment (per-protocol analysis, negative binomial regression). The difference in the number of episodes of vomiting for the ginger versus the placebo arm was −0.54 (P = 0.08) at day 1 and −0.64 (P = 0.003) at day 2.

3.5 | Other outcomes

The other outcomes were analysed using per-protocol analysis and are reported as descriptive statistics only. The median (IQR) volume of ORS assumed by the children in the 4 h after the first dose of treatment was 30 (15; 40) ml/kg in the ginger arm and 10 (5; 25) ml/kg in the placebo arm. The number of children refusing ORS was 17 (24%) in the ginger arm and 37 (52%) in the placebo arm. The number of children

with diarrhea after 24 h, 48 h and 72 h from the first dose of treatment was 38 (54%), 30 (43%) and 7 (10%) in the ginger arm, and 36 (51%), 30 (42%), 13 (18%) in the placebo arm. Intravenous fluid rehydration or hospitalisation were not required for any child. The number of children not attending school 24 h, 48 h and 72 h after the first dose of treatment was 39 (56%), 31 (44%) and 20 (29%) in the ginger arm, and 57 (80%), 40 (56%) and 21 (30%) in the placebo arm.

3.6 | Compliance

The intervention was well accepted by the children as confirmed by an adherence rate of 100%.

3.7 | Adverse effects

There were no reported adverse effects attributable placebo or ginger.

4 | DISCUSSION

To the best of our knowledge, this is the first RCT aimed at evaluating the antiemetic effect of ginger at reducing vomiting in children with AGE. We found that, even under the worst-case scenario ITT, ginger was able to reduce AGE-associated vomiting.

The present study has several strengths. The main strength is that it is a randomised, double-blind, placebo-controlled trial performed by

family pediatricians, which is expected to increase its generalizability as compared to trials performed in tertiary care centers. The second strength is that the ARR of vomiting attributable to ginger is clinically relevant,[29] ranging from −15% under worst-case scenario ITT to −20%

TABLE 2 Baseline features of the placebo and ginger arms

	Placebo (n = 75)	Ginger (n = 75)
Male gender, n (%)	36 (48)	39 (52)
Age (years)	6 (4; 9)	5 (3; 7)
Cesarean delivery, n (%)	44 (59)	49 (65)
Gestational age (weeks)	39 (38; 40)	39 (38; 40)
Breastfeeding, n (%)	47 (63)	40 (53)
Breastfeeding duration (months)	6 (3; 9)	4 (3; 7)
Age at weaning (months)	4 (4; 5)	4 (4; 5)
Vomiting (episodes in the previous 4 h)	4 (3; 5)	4 (3; 5)
Diarrhea (bowel movements in the previous 4 h)	1 (1; 1)	1 (1; 2)
Body weight (kg)	23 (15; 31)	19 (15; 27)
Body weight (SDS WHO)	0.55 (0.01; 0.94)	0.66 (−0.08; 1.15)
Height (m)	1.16 (1.03; 1.31)	1.06 (0.98; 1.25)
Height (SDS WHO)	−0.08 (−0.41; 0.19)	0.16 (−0.28; 0.46)
BMI (kg/m^2)	17 (16; 19)	17 (16; 19)
BMI (SDS WHO)	0.81 (0.26; 1.33)	0.83 (0.02; 1.54)

Note: Continuous variables are reported as median (50th percentile) and interquartile range (IQR, 25th and 75th percentiles). Discrete variables are reported as the number and proportion of subjects with the characteristic of interest.

Abbreviations: BMI, body mass index; SDS, standard deviation scores; WHO, World Health Organization.

under equal-case scenario ITT. Of course, the 95% CI of the NNT is wider under the worst-case scenario but even under this extreme and unlikely scenario, ginger preserves a clinically relevant mean effect size. Moreover, ginger is cheap and this increases its attractiveness for the treatment of AGE-associated vomiting in children.

The present study has nonetheless some limitations. First, we did not collect any data on AGE-associated nausea. Second, mostly for ethical reasons, we did not study children with severe dehydration. Third, we tested only a specific preparation of ginger at a fixed dose. Studies using different doses of standardized extracts are needed to determine the best preparation and dose of ginger for children with AGE.

As the primary outcome is concerned, we found that ginger is effective at preventing the occurrence of at least one episode of vomiting. Our finding that ginger is effective at improving vomiting in children with AGE is in line with studies performed in pregnant women and adults receiving chemotherapy.[38,39] Additional insights on the effect of ginger on pediatric AGE can be obtained from the analysis of the secondary and tertiary outcomes, although they must be taken as exploratory. Most importantly, the administration of ginger was associated with a higher intake of ORS, and with a reduction in the number of school days lost by the children.

Besides its general anti-inflammatory effect [40] ginger contains volatile phenolic compounds such as gingerols and shogaol, that may reduce vomiting by different mechanisms.[41] In animal models, 6-, 8-, and 10-gingerols, and 6-shogaol are active on M3 receptors, 5-HT$_3$ receptors (guinea pigs), and 5-HT$_4$ receptors (rats). Gingerols and shogaol may exert their anti-emetic effect by acting on the 5-HT$_3$ receptor ion-channel complex, possibly binding to a modulatory site distinct from the serotonin binding site. This may produce indirect effects on the signal cascade behind the 5-HT$_3$ receptor channel complex through substance P and muscarinic receptors.[41] More recently, it was shown that the antiemetic effect of ginger may be

TABLE 3 Incidence of the primary outcome in the ginger and placebo arms

	ITT equal case scenario	ITT worst-case scenario	PPA
Placebo event rate placebo	65/75 0.87 [0.79 to 0.94]	61/75 0.81 [0.73 to 0.90]	61/71 0.86 [0.78 to 0.94]
Ginger event rate ginger	50/75 0.67 [0.56 to 0.77]	50/75 0.67 [0.56 to 0.77]	45/70 0.64 [0.53 to 0.76]
Absolute risk reduction (ginger-placebo)	−0.20[a] [−0.33 to −0.07] P = 0.003 (Wald)	−15[a] [−0.29 to −0.006] P = 0.038 (Wald)	−0.22[a] [−0.35 to −0.08] P = 0.002 (Wald)
Number needed to treat	5[b] [3 to 15]	7[b] [4 to 167]	5[b] [3 to 14]
Number of children	150	150	141

Note: Values are proportions and 95% confidence interval (in square brackets) from binomial regression. The ITT "equal case scenario" analysis assumes the occurrence of the best outcome (no vomiting) in the 5 children lost to follow-up in the ginger arm and of the same outcome (no vomiting) in the 4 children lost to follow-up in the placebo arm. The ITT "worst case scenario" analysis assumes the occurrence of the worst outcome (vomiting) in the 5 children lost to follow-up in the ginger arm and of the best outcome (no vomiting) in the 4 children lost to follow-up in the placebo arm.

Abbreviations: ITT, intention-to treat analysis; PPA, per-protocol analysis.

[a]95 confidence interval calculated from binomial regression.

[b]95 confidence interval calculated from Bender's formula.

TABLE 4 Incidence of vomiting 24 and 48 h after the first dose of treatment (secondary outcome, per-protocol analysis)

	24 h after the first dose of treatment	48 h after the first dose of treatment
Placebo event rate	61/71 0.86 [0.78 to 0.94]	41/71 0.58 [0.46 to 0.69]
Ginger event rate	45/70 0.64 [0.53 to 0.76]	27/70 0.39 [0.27 to 0.50]
Absolute risk reduction (ginger-placebo)	−0.22 [−0.38 to −0.06][a] $P = 0.005$ (Wald)[b]	−0.19 [−0.38 to −0.01][a] P[b] $= 0.04$ (Wald)[b]

Note: Values are proportions and 95% confidence intervals (in square brackets) from binomial regression.
[a]Bonferroni's corrected 95% confidence interval (correction for two comparisons).
[b]Bonferroni's corrected *p* value (correction for two comparisons).

TABLE 5 Number of episodes of vomiting 24 and 48 h after the first dose of treatment (secondary outcome, per-protocol analysis)

	24 h after the first dose of treatment	48 h after the first dose of treatment
Number of episodes of vomiting—placebo	2.03 [1.67 to 2.39]	1.18 [0.85 to 1.52]
Number of episodes of vomiting—ginger	1.49 [1.12 to 1.86]	0.54 [0.33 to 0.75]
Difference in the number of episodes of vomiting (ginger-placebo)	−0.54 [−1.13 to 0.05][a] $P = 0.08$ (Wald)[b]	−0.64 [−1.09 to −0.19][a] $P = 0.003$ (Wald)[a]

Note: Values are means and 95% confidence intervals (in square brackets) calculated from negative binomial regression.
[a]Bonferroni's corrected 95% confidence interval (correction for two comparisons).
[b]Bonferroni's corrected *P* value (correction for two comparisons).

partly dependent upon its modulating effect on the vagal nociceptive receptors of the gastrointestinal tract.[42]

In conclusion, we found that ginger is effective at reducing vomiting in children with AGE. Further clinical trials are warranted to confirm our findings, to define the most effective dose of ginger, and to test whether ginger could be effective at improving vomiting of different etiologies in childhood.

AUTHORSHIP

Guarantor of the article: None.

Author contributions: RN, GC and RBC designed the study, coordinated the research team and reviewed the manuscript; RN, GB and RBC drafted the manuscript and had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis; RN, GC, MM, PF, GDM and MR cared for the children; RN and GB performed statistical analysis. All authors had access to the study data, reviewed and approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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