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The efficacy of ginger for the prevention of postoperative nausea and vomiting: A meta-analysis

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KEY WORDS

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Objective: The aim of this study was to specifically determine the impact of a fixed dose of ginger administration, compared with placebo, on the 24-hour postoperative nausea and vomiting.

Study design: The design was a systematic review and metaanalysis of trials revealed by searches. Randomized controlled trials comparing ginger with placebo to prevent postoperative nausea and vomiting and postoperative vomiting from Medline, IPA, CINAHL, Cochrane CENTRAL, HealthStar, Current Contents, bibliographies of retrieved articles, contact of authors, and experts in the field. Two reviewers selected studies for inclusion and independently extracted data.

Results: Five randomized trials including a total of 363 patients were pooled for analysis of preventing postoperative nausea and vomiting and postoperative vomiting. The summary relative risks of ginger for postoperative nausea and vomiting and postoperative vomiting were 0.69 (95% confidence interval 0.54 to 0.89) and 0.61 (95% confidence interval 0.45 to 0.84), respectively. Only one side effect, abdominal discomfort, was reported.

Conclusions: This meta-analysis demonstrates that a fixed dose at least 1 g of ginger is more effective than placebo for the prevention of postoperative nausea and vomiting and postoperative vomiting. Use of ginger is an effective means for reducing postoperative nausea and vomiting.

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Postoperative nausea and vomiting (PONV) is one of the most common side effects associated with surgical procedures.¹⁻⁹ The incidence of PONV ranges from 1%

to 43%.^{1,2,4,7,8} Several factors affecting PONV include types of surgical procedures, anesthetic methods, gender, age, obesity, preoperative eating patterns, and history of PONV or morning sickness.^{1,2,4-8} PONV is a very distressing outcome, which may lead to medical complications such as wound disruption, esophageal tears, gastric herniation, fatigue, dehydration, and possibly electrolyte imbalances.^{1-3,7} PONV is also associated with increased costs of care because of increased length of hospital stay.^{1,7,8} Despite a large number of

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studies being conducted to investigate the efficacy of various antiemetics, no intervention has been proved to be universally effective and accepted as a gold standard for the prevention of PONV.⁷⁻¹⁰

Ginger (*Zingiber officinale*) has traditionally been used in China for gastrointestinal symptoms such as nausea and vomiting.¹¹⁻¹⁴ Recent evidences suggest that its antiemetic activities may be derived from its antiserotonin-3 effects on both central nervous and gastrointestinal systems.^{11,12,14-17} During the past decade, several randomized, placebo-controlled trials have been conducted to evaluate the effectiveness of ginger in the prevention of PONV.^{12-14,18-21} A systematic review was recently published.²² However, the included studies were clinically heterogeneous in terms of various dose regimens and different timing for outcome assessment. In addition, a recent unpublished study conducted in Thailand was not included.¹² The purpose of this study was to specifically determine the impact a fixed dose of ginger administration on the 24-hour PONV.

Material and methods

Search strategy

We searched the following databases: Medline, IPA, CINAHL, Cochrane CENTRAL, HealthStar, Current Contents, bibliographies of retrieved articles; we also contacted pharmaceutical companies, authors, and experts in the field. Key words for searching were ginger, *Zingiber officinale*, ingwer, ingber, nausea, vomiting, and postoperative nausea and vomiting. There was no language restriction.

Criteria for trial inclusion

Trials must meet the following inclusion criteria: (1) randomized, placebo-controlled trials evaluating antiemetic effects of ginger for the prevention of postoperative nausea and/or vomiting; (2) 1 g or more of ginger was administered; and (3) providing sufficient data to calculate the incidence of 24-hour PONV or postoperative vomiting (POV).

Assessment of methodological quality

The methodological quality of each trial was assessed by 2 reviewers using a scale developed by Jadad et al.²³ Disagreements in quality of studies were resolved by discussion. Items for methodology evaluation include random allocation, blinding, and description of drop-outs and withdrawals. We also determined whether the investigators assayed the amount of active ingredients in each ginger preparation.

Data extraction and summarizing study results

Study characteristics and results were extracted by 2 independent reviewers. We extracted the number and characteristics of patients, the amount of ginger administered, surgical procedures, duration of surgery, types of anesthesia, incidence of PONV or POV, and outcome measurement.

Analyses

For analyses comparing ginger with placebo, we calculated the overall relative risk and 95% confidence intervals using the method of DerSimonian and Liard²⁴ under a random-effects model. Heterogeneity was assessed by the Mantel-Haenszel method. A publication bias was assessed using a funnel plot method; asymmetrical shape indicated an existence of bias.

Results

Our search yielded a total of 59 potential studies. Fifty-three studies were excluded because they were not randomized, placebo-controlled trials. We identified a recent unpublished study in Thailand by contacting an expert.¹²

The study by Arfeen et al¹⁸ was excluded because only the incidence of 3-hour PONV was reported. The study by Eberhart et al¹⁹ was also excluded because the amount of ginger administered was only 0.3 or 0.6 g. Finally, we included a total of 5 studies involving 363 patients in our data analysis.^{12-14,20,21}

Table I gives an overview of the 5 included^{12-14,20,21} and 2 excluded trials.^{18,19} All studies were randomized, double-blinded, placebo-controlled trials. JADAD scores²⁴ of all 5 trials included in the analysis ranged from 3 to 4. In 3 studies, types of surgery performed were outpatient gynecological laparoscopy.^{13,20,21} Twenty-eight percent of surgery performed in the study by Bone and colleagues¹⁴ were abdominal gynecological laparoscopy, whereas the remaining received other types of major gynecological surgery. Only lower extremity surgery was performed in the study by Janngam.¹²

Patients' ages were comparable among studies, ranging from 31 to 46 years.^{12-14,20,21} The mean weight of patients included in 2 studies was approximately 51 to 53 kg,^{13,20} whereas those in other studies were more than 60 kg.^{12,14,21} The percentage of patients with history of PONV in the study of Visalyaputra and colleagues¹³ was 7% and 14% in the ginger and the placebo groups, respectively. These percentages were much lower than those reported in the other 2 studies.^{12,21} The mean duration of gynecological surgery ranges from 20 to 72 minutes, whereas the mean duration of low extremity surgery was between 100 and 115 minutes.^{12-14,20,21}

Table I Description of randomized, double-blind, controlled trials of ginger for PONV and POV

	JADAD	Intervention	Dose (g)	Characteristic of patients			Surgery types	Duration of surgery (minutes)	History of PONV (%)	Total morphine (mg)	Assessment Time (hour)
				n	Age (yr)	Weight (kg)					
Included trials											
Bone et al ¹⁴ (1990)	3	Ginger	1	20	39.5	62.8	Mixed	58.3	40	N/A	—
		Placebo		20	45.7	60.6		51.7	35	N/A	
Phillips and Hutchinson ²¹ (1993)	3	Ginger	1	40	35	67	Laparoscopic	25	30	N/A	PONV
		Placebo		40	31	66	Gynecological	25	25	N/A	POV
Visalyaputra et al ¹³ (1998)	3	Ginger	2	27	32	51	Laparoscopic	20	7	N/A	—
		Placebo		28	33	51	Gynecological	41	14	N/A	POV
Pongrojpraw and Chiamchanya ²⁰ (2003)	3	Ginger	1	40	32	53.1	Laparoscopic	71.75	N/A	0	PONV
		Placebo		40	34	52.3	Gynecological	69.13	N/A	0	POV
Janngam ¹² (2003)	4	Ginger	1	54	37.6	61.2	Low-extremity surgery	100	N/A	0.2	PONV
		Placebo		54	35.1	61.1			114.81	N/A	0.2
Excluded trials											
Arfeen et al ¹⁸ (1995)	4	Ginger	0.5-1	36	31.8	66.2	Laparoscopic	34	39	11.3	PONV
		Placebo		36	32	64.2	gynecological	34	33	11.9	POV
Eberhart et al ¹⁹ (2003)	4	Ginger	0.3-0.6	57	38	N/A	Laparoscopic	60	25	N/A	PONV
		Placebo		59	37	N/A	gynecological	60	27	N/A	POV

N/A, Not available.

All subjects were randomly allocated into the treatment or control groups. The treatment group was given 1 g of ginger, and the control group received placebo. Both were given to subjects 1 hour before the induction of anesthesia.^{12-14,20,21} In only the study of Vislyaputra and colleagues,¹³ an additional gram of either ginger or placebo was administered before discharge. None of the included studies reported the amount of active ingredients or the quality of ginger preparation.

The amount of anesthesia given in these studies was minimal, thus having negligible effect on the risk of PONV. All studies reported the incidence of POV,^{12-14,20,21} and only 3 studies reported the incidence of PONV.^{12,20,21}

Efficacy and sensitivity analyses

Ginger was significantly better than placebo for the prevention of PONV and POV (Table II and the Figure). The summary relative risk of ginger for PONV was 0.65 (95% confidence interval [CI] 0.51 to 0.84) and for POV was 0.62 (95% CI 0.46 to 0.84). Only 1 side effect, abdominal discomfort, was reported in the study of Pongrojpraw and Chiamchanya.²⁰

In sensitivity analyses, we included the study of Eberhart et al¹⁹ and found that the summary relative risk reduction of ginger for PONV remained statistically significant. (relative risk 0.74 [95% CI 0.56 to 0.98]). The summary relative risk of ginger for POV was 0.75 (95% CI 0.52 to 1.07).

Comment

This study summarizes evidence from randomized, placebo-controlled trials evaluating the effectiveness of ginger for the prevention of PONV. We found that the incidence of PONV and POV in the ginger arm is 35% and 38%, respectively, lower than those in the placebo arm. Based on these findings, we conclude that ginger at a dose of 1 g or greater can significantly reduce the incidence of 24-hour PONV in patients undergoing gynecological and lower extremity surgery.

A systematic review by Morin et al²² evaluating the effect of ginger on PONV was recently published. They included 6 randomized controlled trials involving 538 patients in the final analysis. The investigators reported a pooled relative risk of PONV with ginger as 0.84 (95% CI 0.69 to 1.03), compared with placebo, and concluded that ginger is not a clinically relevant antiemetic in the PONV setting.²² Our study, however, found contradicting results. The main differences between the previously published systematic review and our study are the study inclusion criteria and the addition of a recent unpublished randomized, placebo-controlled trial conducted by Janngam.¹² Our study selection criteria help reduce heterogeneity among trials, especially on the dose of ginger and outcome of interest. The issue of dose is very important because difference in doses of a drug or intervention may result in different outcomes. In addition, we used the first 24-hour PONV to avoid differences in timing of outcome measurement. By allowing only

Table II Overall outcomes of meta-analysis measured in clinical trial of ginger

	POV, n/n (%)		Relative risk (95% CI)	PONV, n/n (%)		Relative risk (95% CI)
	Ginger	Control		Ginger	Control	
Bone et al ¹⁴ (1990)	9/20 (45.0)	14/20 (70.0)	0.64 (0.37-1.13)	N/A	N/A	N/A
Phillips and Hutchinson ²¹ (1993)	4/40 (10.0)	9/40 (22.5)	0.44 (0.15-1.33)	19/40 (47.5)	25/40 (62.5)	0.76 (0.51-1.14)
Visalyaputra et al ¹³ (1998)	7/27 (25.9)	10/28 (35.7)	0.73 (0.32-1.63)	N/A	N/A	N/A
Pongprojpaw and Chiamchanya ²⁰ (2003)	7/40 (17.5)	12/40 (30.0)	0.58 (0.26-1.33)	12/40 (30.0)	23/40 (57.5)	0.52 (0.30-0.90)
Janngam ¹² (2003)	15/54 (27.8)	24/54 (44.4)	0.62 (0.37-1.05)	21/54 (38.9)	33/54 (61.1)	0.64 (0.43-0.95)
Eberhart et al ¹⁹ (2003)	23/57 (40.3)	16/59 (27.1)	1.49 (0.88-2.51)	30/57 (52.6)	29/57 (50.9)	1.03 (0.73-1.47)
Pooled RR (excluding Eberhart et al)			0.62 (0.46-0.84)			0.65 (0.51-0.84)
Pooled RR (including Eberhart et al.)			0.75 (0.52-1.07)			0.74 (0.56-0.98)

RR, Relative risk; N/A, not available.

studies using similar doses of ginger and outcome measurements into data analysis, a more reliable measure of ginger's efficacy on a specific outcome can be determined.

Certain limitations in our study exist. Although we specifically evaluated the effect of 1 g or more of ginger, the amount of active ingredients may still vary. Because the active ingredients in ginger are unknown, there is no standardized assay to quantify the amount of those ingredients in ginger preparations used in the included studies. However, ginger used in the included studies was prepared using similar production technique (ginger root powder).

Our study findings remain significant, even though a study using different production techniques was included. In a sensitivity analysis including the study by Eberhart et al¹⁹ in which ginger extract (using acetone as an extracting agent) was used, the summary relative risk reduction of ginger for PONV remains statistically significant with a relative risk of 0.74 (95% CI 0.56 to 0.98).^{12,20,21} The summary relative risk of ginger for POV was 0.75 (95% CI 0.52 to 1.07).^{12-14,19-21}

Despite including more homogenous studies in the analysis, certain heterogeneity may still exist in our study, especially patient population and surgical interventions. Interpreting antiemetic effects of ginger may be difficult on the basis of these factors. Lastly, although we have exhausted our effort in the literature search, there might be unpublished reports that we were unable to identify.

Placebo-controlled trials are generally required to show an effectiveness or lack of effectiveness of a certain intervention. However, because treatment of PONV is generally given on an empirical basis, comparison of ginger with medications commonly given for PONV may provide valuable information in the effect of ginger in relation to those treatments. Among 5 studies included in our analysis,^{12-14,20,21} 2 studies also had comparators other than placebo including metoclopramide and droperidol.^{13,14} However, because of the

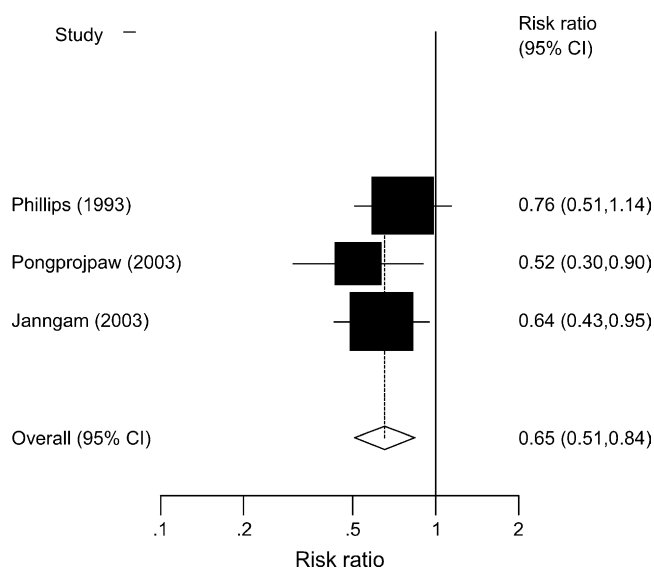


Figure Relative risk reported (95% CIs) of ginger in antiemetic effects for prevention of PONV.^{12,20,21}

small number of patients, any firm conclusion cannot be drawn from these studies.

The antiemetic effects of ginger might be explained by several mechanisms. Recent animal models and in vitro studies have demonstrated that ginger extract possesses antiserotonergic and 5-HT₃ receptor antagonism effects, which play an important role in the etiology of PONV.^{15,25,26} In addition, gingerols and shogaols, potentially active constituents in ginger extract, have been shown to affect gastric motility.^{27,28} A recent in vitro study²⁹ showed that ginger is able to reduce electrical stimulation and acetylcholine-evoked contractions in rat isolated ileum. The ability of ginger to inhibit contraction by exogenous administration of acetylcholine suggests that ginger has a direct antispasmodic effect. Although ginger's inhibitory effect remained intact with blockades of α_2 -adrenergic, cannabinoid CB₁, and opioid

receptors, it was reduced by capsazepine, a vanilloid receptor antagonist, suggesting an involvement of such receptors on ginger's effect.²⁹ Despite the previously mentioned data, however, the exact mechanism of ginger in the prevention of PONV remains to be elucidated.

With regard to generalizability, we acknowledge that the majority of patients included in this metaanalysis were Asian with an average weight of 50 kg. One potential limitation from the nature of our study population is the issue of dosage adjustment in patients with greater body weight, especially those of Western descendants. Because one third of patients (120 of 363) included in this analysis were Westerners with the average weight of more than 60 kg, this may provide some evidence of effectiveness of ginger in this group of patients. However, randomized, controlled trials designed to specifically address this issue are warranted to make any firm recommendation.

Based on the results of our study, we believe that ginger is an effective therapeutic option in the prevention of PONV. Because of its widespread availability, low cost, and great tolerability profile, ginger may be an attractive option, at least as a component in the combined antiemetic regimen, especially in countries in which cost of care is a major issue. With the availability of more data, the exact role of ginger as an antiemetic in the PONV setting may be elucidated.

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