

2019

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## Recommended Citation

Taurino, Julina, "Is Ginger an Effective Treatment for Reducing the Severity of Chemotherapy-Induced Nausea in Breast Cancer Patients?" (2019). *PCOM Physician Assistant Studies Student Scholarship*. 498.

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**Is Ginger an Effective Treatment for Reducing the Severity of Chemotherapy-Induced Nausea in Breast Cancer Patients?**

Julina Taurino PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences - Physician Assistant

Department of Physician Assistant Studies  
Philadelphia College of Osteopathic Medicine  
Philadelphia, Pennsylvania

December 14, 2018

## **ABSTRACT**

**Objective:** The objective of this selective EBM review is to determine whether or not “Is ginger an effective treatment for reducing the severity of chemotherapy-induced nausea in breast cancer patients?”

**Study Design:** The systematic review of three English language, peer reviewed, randomized control trials have been published between 2015 and 2016.

**Data Sources:** Three randomized control trials were obtained using the PubMed database. One single-blind randomized control trial, one double-blinded randomized control trial, and one double-blind Phase II-III randomized control trial.

**Outcomes Measured:** The participants of the trials graded the severity of nausea after the intervention of ginger or the control. Each study assessed patient-oriented outcomes. The outcomes measured were analyzed via visual analog scale<sup>7,8</sup>, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire<sup>8</sup>, and self-reported severity of nausea questionnaire<sup>6</sup>.

**Results:** All three studies did not show a significant improvement in the severity of nausea in breast cancer patients receiving chemotherapy after the treatment of ginger. However, one study showed a positive benefit in the health-related quality of life after using ginger essential oil aromatherapy.

**Conclusion:** The three randomized control trials used in this systematic review did not show an improvement in the severity of chemotherapy-induced nausea when using ginger as a treatment intervention. There were too many limitations determined in the three control trials which could have cause insignificant results. Although, participants in the single-blinded control trial reported positive improvement in the health-related quality of life.

**Keywords:** Nausea, Chemotherapy, Ginger

## INTRODUCTION

Chemotherapy-induced nausea (CIN) is a common and stressful acute side effect to pharmacologic treatment of cancer. Nausea is a feeling that is subjective and causes disturbance to the digestive tract. Therefore, nausea is a distressing sensation that is typically felt in the posterior pharynx or epigastrium. The onset of nausea has been found to be acute or delayed depending upon the chemotherapy drug.<sup>1</sup> Acute nausea is likely to occur within 24 hours of administration of chemotherapy, while delayed nausea is defined to occur more than 24 hours after administration of chemotherapy.<sup>1</sup> This side effect of chemotherapy drugs provokes a major impact on the lives of cancer patients. This systematic review evaluates the efficacy of ginger as a nonpharmacological treatment to chemotherapy-induced nausea.

According to the National Cancer Institute, the prevalence of CIN occurs in 80% of cancer patients.<sup>1</sup> This common side effect needs to be managed and monitored medically. Cancer patients are managed by a medical team, one which includes physician assistants (PAs). As of 2017, there were 1355 PAs with a career in oncology.<sup>2</sup> Out of that number, 70.5% of those PAs provided services for diagnosis, treatment, and management of cancer as a chronic illness.<sup>2</sup>

Chemotherapy can treat many cancers, however this systematic review analyzed studies involving breast cancer patients. As of 2012, there were 3 million women living with breast cancer in America which all require healthcare visits.<sup>3</sup> Each healthcare visit has a cost and the exact cost of treatment depends on the stage of cancer. The stages include 0, I, II, III, and IV which can cost anywhere from \$71,909 to \$182,655 for treatment.<sup>3</sup> Overall, the cost is higher for patients with an advanced cancer at diagnosis.<sup>3</sup>

There has been significant progress at understanding the cause of CIN. The sensation of nausea is controlled neurologically by the central nervous system, specifically autonomic nerves.<sup>1</sup> It is known that areas of the brain such as the cerebral cortex, limbic system, activation of chemoreceptor trigger zones, and the vestibular-labyrinthine are all involved in producing a nauseous sensation.<sup>1</sup> It is known that the dose, route of administration, and schedule of chemotherapy drugs all can contribute to CIN.<sup>4</sup> In addition, patients younger than 50 years old, women, a history of alcohol abuse, and history of motion sickness are more likely to experience CIN.<sup>1</sup> While cancer does not have a definite cure, patients will need to receive a chemotherapy depending on the severity of the cancer and it is possible to experience nausea a side effect.

The treatment of CIN is classically managed with pharmacologic therapies known as anti-emetics. This group of drugs work by blocking specific neurotransmitters that are otherwise known to activate the chemoreceptor trigger zones. Some of the neurotransmitters include serotonin, histamine, acetylcholine, and dopamine.<sup>1</sup> Medications to treat CIN include ondansetron, granisetron, metoclopramide, and dexamethasone.<sup>1</sup> Many anti-emetic drugs are used in combination depending upon how high the risk that nausea will be produced by the chemotherapy drug. Anti-emetic medications can be administered via oral pills, parenteral injection, transdermal patch, and rectal suppository.

This systematic review analyzes three randomized control trials that use ginger as a non-pharmacological treatment for CIN to improve patients' quality of life. Ginger is considered to be used as a natural alternative to relieve CIN in patients that do not desire pharmacological drugs or patients who are resistant to those drugs. Ginger is a form of herbal therapy that has been used for thousands of years in cultures such as ancient China and India.<sup>5</sup> This earth-produced plant has been used in studies to treat cancer, diabetes mellitus, inflammation, vomiting, and nausea.<sup>5</sup>

## **OBJECTIVE**

The objective of this EBM review is to determine whether or not “Is ginger an effective treatment for reducing the severity of chemotherapy-induced nausea in breast cancer patients?”

## **METHODS**

The studies used in this systematic review are all randomized control trials found on PubMed. The population of all three studies included female patients diagnosed with breast cancer who experienced nausea as a symptom caused by chemotherapy. The patient population included in the studies were over 18 years old. The intervention used in all the studies was ginger. Ansari et Al. and Thamlikitikul et Al. both used a 500-mg ginger capsule.<sup>6,7</sup> However, Lua et Al. used ginger aromatherapy.<sup>8</sup> The comparison group in all studies used a visually matched placebo as the control. The outcome measured was determined by the efficacy of ginger by rating the severity of nausea and determining the health-related quality of life.

The key words used during the research of this systematic review included “ginger”, “nausea”, “chemotherapy”, and “breast cancer”. The studies were all selected by pertinence of the clinical question from the PubMed database. Each study has been published in peer reviewed journals in the English language. The studies selected for this systematic review included outcomes that were patient-oriented. The inclusion criteria incorporated the studies needed to be randomized, controlled, blinded, published after 2010, and with patient oriented outcomes. The participants needed to be diagnosed with breast cancer, receiving chemotherapy, and experiencing nausea. The exclusion criteria included participants under the age of 18 and a diagnosis other malignancies. The statistics reported include ANOVA, p-value, RBI, ABI, and NNT. Table 1 consists of demographics and characteristics of the studies used in this review.

Table 1: Demographics &amp; Characteristics of the studies in this systematic review

Study	Type	# Pts	Ages (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Ansari <sup>6</sup> (2016)	Double-Blind, Phase II-III, RCT	150	48.6 (25-79)	-Diagnosed breast cancer -Receiving AC, CAF, TAC chemotherapy -At least 3 chemotherapy cycles	-History of previous malignancy or chemotherapy -History of another systematic disease, metastatic condition, or receiving antiemetic drugs	31	500 mg ginger powder BID for 3 days
Lua <sup>8</sup> (2015)	Single-blind RCT	75	47.3 ±9.26	-Women >18 -Normal sense of smell -Diagnosed with breast cancer and receiving chemotherapy -at least two chemotherapy courses remaining	-Pts with other malignancies -Pts allergic to ginger, perfumes, or cosmetics -Pts undergoing radiation therapy	15	Breathe deeply into aromatherapy necklace at least 3 times a day for at least 3 periods of 2 minutes
Tham-likitkul <sup>7</sup> (2017)	Double-blind RCT	34	>18 years old	- >18 years old -diagnosed with breast cancer -experienced vomiting or nausea -received first cycle of chemotherapy -at least two cycles chemotherapy	-Pregnant -Lactating -Nausea/ vomiting prior to chemotherapy -Bleeding diathesis -ginger allergy -concomitant treatment with other chemotherapy - other conditions that cause nausea/ vomiting	1	500 mg ginger capsule BID for 5 days starting the first day of the second chemotherapy cycle

## **OUTCOMES MEASURED**

The outcomes measured in the systematic review used three randomized control trials that assessed patient oriented outcomes (POEMS). The control trials analyzed ginger as a treatment to manage nausea as a result of chemotherapy drugs. Lua et Al. used a visual analog scale (VAS) to measure the severity of nausea.<sup>8</sup> Also, Lua et Al. measured participants health related quality of life (HRQoL) while experiencing CIN by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaires (EORTC QLQ-C30).<sup>8</sup> Ansari et Al. used participant reported adverse events that occurred during the study period.<sup>6</sup> Thamlikitikul et Al. used a questionnaire to record severity which included a VAS.<sup>7</sup>

## **RESULTS**

This systematic review used three randomized control trials to determine if ginger could improve the severity of nausea produced by chemotherapy and enhance quality of life in breast cancer patients. Each trial evaluated the severity of nausea differently. There are two trials that contain dichotomous data and one trial that has continuous data.

Ansari et Al. studied 150 patients that were recently diagnosed with breast cancer and would receive chemotherapy in Iran. The participants were randomly separated by a radiation oncology resident into two groups of ginger (n=75) and control (n=75).<sup>6</sup> The patients along with the attending oncologists were unaware of the content within the capsule. The inclusion and exclusion criteria of Ansari et Al. study is shown in Table 1. Participants in the experimental and control group were asked to consume two capsules every 12 hours for 3 days.<sup>6</sup> The participants were instructed to self-record severity of nausea during each chemotherapy cycle. Nausea was graded by no nausea or nausea with three levels of severity.

At the conclusion of the study, 31 patients were not accounted for in the results.<sup>6</sup> This group of patients did not properly record severity of nausea on most days. The participants forgot to record their symptoms and were excluded from the study. However, 119 participants were included in the experimental (n=57) and the control (n=62) with appropriate recordings of nausea severity.<sup>6</sup>

The results of Ansari et Al. study concluded that the intervention was not statistically significant. The author of this systematic review converted continuous data to dichotomous for the third cycle of chemotherapy results. The study gave the number of subjects that in the control arm and the ginger arm whom did not experience nausea. The control arm that scored 0 consisted of 20 out of 62 subjects.<sup>6</sup> While the ginger arm scored 0 was 23 out of 57 subjects.<sup>6</sup> RBI, ABI, and NNT are calculated in Table 2. For this treatment to show effectiveness, there would need to be 13 patients treated for 1 more patient to experience relief of nausea with a ginger intervention which is a small treatment effect. The study provided the mean nausea severity scores which was 1.40 for ginger and 1.42 for control that produced a difference of 0.02 between the ginger and placebo.<sup>6</sup> This result showed nausea was more severe in the ginger arm however, this is not considered significant.<sup>6</sup>

Table 2: Calculation for treatment of Ansair et Al.<sup>6</sup>

Study	CER	EER	RBI	ABI	NNT
Ansari et Al.	32%	40%	25%	8%	13

Thamlikitkul et Al. double-blind study consisted of only 34 participants and the study was conducted in Thailand. Each participant was assigned to a group by a stratified randomization table.<sup>7</sup> The study consisted of a ginger group (n=19) and control group (n=15).<sup>7</sup> However, the groups were switched

in the next cycle of chemotherapy to receive the opposite intervention. Although one participant did not fully complete the intervention, no participants were excluded from the study.<sup>7</sup> The intervention of Thamlikitkul et Al. consisted of participants consuming a 500-mg ginger capsule or placebo twice a day for five days which started on the first day of the chemotherapy cycle.<sup>7</sup> The participants of this study were prophylactically treated with anti-emetics and were allowed to use rescue anti-emetics if symptoms became intolerable.<sup>7</sup>

The results of Thamlikitkul et Al. study found that the primary outcome of that study was not a significant difference between the ginger and the control.<sup>7</sup> The data from this study was presented as continuous and not able to be converted to dichotomous. Thamlikitkul et Al. collected data via VAS and presented the data as a change in mean from the baseline<sup>7</sup>. The study used ANOVA test to determine the difference in nausea score. The results of the study are represented in Table 3. The interpretation of the results displays a mean nausea score of 3 with a small treatment effect of this trial.<sup>7</sup> There showed no significance difference of acute or delayed nausea in both arms of the study.<sup>7</sup>

Table 3: Thamlikitkul et Al. study that used ginger used as a treatment for CIN in comparison to a placebo of the primary outcome<sup>7</sup>

Thamlikitkul et Al.	CI	P value
Ginger vs. Control rating severity of nausea	95%, -3 to 9	p=0.30

Lua et Al. enrolled 75 participants that were diagnosed with breast cancer and receiving chemotherapy into a single-blind study which took place in Malaysia.<sup>8</sup> The subjects were randomized into two groups by using a technique known as block randomization 1:1 ratio.<sup>8</sup> The inclusion and exclusion criteria of this study is displayed in Table 1. The placebo group consisted

of 37 participants and the ginger intervention group consisted on 38 participants.<sup>8</sup> The intervention of Lua et Al. study used ginger essential oil to treat CIN. In the comparison group, the placebo was a fragranced matched oil. Participants were instructed to wear a necklace for 5 days and breathe deeply three times a day with the oil bottle under the nose for 2-minute duration.<sup>8</sup> The groups interventions were crossed over to the opposite intervention on the second round of chemotherapy. Lua et Al. collected data by providing a VAS for the participants to record the severity of nausea within a diary. The participants were instructed to self-record severity of nausea three times a day, 9 am, 3 pm, and 9 pm respectively.<sup>8</sup> At the end of the study, a total of 60 participants from each group were accounted for in the results of the study with 30 subjects in each arm.<sup>8</sup>

The results of Lua et Al. determined that the treatment of ginger essential oil showed no significant difference on the VAS score of nausea.<sup>8</sup> The results were presented in continuous data in the trial and could not be converted to dichotomous. Lua et Al. reported five days of data via ANOVA to determine the difference in severity of nausea between the two interventions.<sup>8</sup> The results are displayed in Table 4 of this systematic review. The interpretation of the results shows a mean difference of 1.83 between the essential oil and fragranced oil which is a small treatment effect.<sup>8</sup>

Table 4: Ginger as an essential oil vs. a fragranced oil for the treatments of CIN

Study: Lua et Al.	<i>F</i> stat	P value
Ginger Essential oil vs. fragranced oil	$F(1, 58) = 1.82$	P=0.183

Lua et Al. used a patient oriented questionnaire to determine the HRQoL profile of the breast cancer participants. The questionnaire EORTC QLQ-30 analyzed five areas of functioning

and eight symptoms associated with chemotherapy cycles.<sup>8</sup> Specifically, nausea and vomiting were grouped together on the HRQoL scale. The results showed a significant difference of reduction in symptoms while participants were using the ginger essential oil intervention.<sup>8</sup> The results reported a  $p < 0.001$  which is significant<sup>8</sup>.

Ginger as a treatment intervention was well tolerated across all studies. Participants in all of the studies did not have any negative reactions to ginger.

## **DISCUSSION**

Chemotherapy is a treatment for cancer and it can produce nausea as a side effect that can decrease the quality of life in patients. This selective EBM systematic review analyzed whether or not ginger is an effective treatment to reduce the severity of nausea cause by chemotherapy. All three randomized control trials evaluated in this review showed ginger is not a significant treatment for CIN. However, the HRQoL profile measured in the study produced by Lua et Al. showed an increase of the quality of life in patients experiencing nausea and vomiting as a symptom produced by chemotherapy.

Ginger has been used traditionally for centuries and it can be easily found in markets across the globe.<sup>5</sup> The earth-produced plant rarely causes adverse reactions unless it is consumed in in large doses.<sup>5</sup> The recommended dosing for nausea is ranged between 250 mg to 2 grams a day divided over three to four times a day.<sup>5</sup> Ginger has the potential for interaction with medications such as anti-platelets, anticoagulants, antihypertensive, hypoglycemic agents, nonsteroidal anti-inflammatory drugs, salicylates, and thrombolytic agents.<sup>5</sup> However, there are no contraindications identified for individuals using ginger.<sup>5</sup>

This systematic review used three randomized control trials to determine if ginger can improve nausea as a side effect to patients receiving chemotherapy. Although each trial found data with insignificant results, it does not exclude ginger as a treatment. This non-pharmalogical treatment should not be excluded because there were many limitations to the studies which could have manipulated the results. Therefore, it would be beneficial if future clinical trials used ginger with different parameters than the studies of this systematic review.

Additionally, each study contained limitations which include population size, time period, and recording of symptoms. Thamlikitkul et Al. study was limited by the sample size which consisted of only 34 participants.<sup>7</sup> In the next study conducted by Ansari et Al., the time period of treatment only lasted for 3 days.<sup>6</sup> It is possible that ginger needs a longer treatment time to see a decrease in nausea severity. Finally, the study conducted by Lua et Al. allowed patients to self-record symptoms which could have skewed the results of the study.<sup>8</sup> It would be more accurate with computers tracking when patients record their symptoms.

Another limiting factor, each study used in the review was conducted within another country outside of the United States. These countries include Iran, Thailand, and Malaysia. The standards in these countries may not be consistent with those in America which puts a limitation of the results. Therefore, the standards of treatment within the United States could possibly change the results if future trials are conducted here.

The final limitation includes prophylactic treatment of CIN with anti-emetic medications to the participants in the study. Although medical practice does not inflict harm on patients that seek treatment, the administration of anti-emetics prior to chemotherapy could have influenced the results. In the studies conducted by Thamlikitkul et Al. and Lua et Al., the participants were prophylactically treat with anti-emetics.<sup>7,8</sup>

## **CONCLUSION**

The evidence evaluated in this systematic review found that ginger is not effective at improving the severity of nausea produced by chemotherapy. The study conducted by Lua et Al. found that the health-related quality of life showed significant improvement of nausea and vomiting ( $p < 0.001$ ) by ginger essential oil aromatherapy via the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire.<sup>8</sup> However, each of the control trials did not find any significant improvement to the severity of nausea during the intervention compared to the control group. Since there are multiple limitations to these control trials, ginger as a treatment for CIN should not be excluded as a for a future intervention. New research trials to investigate the potential of ginger would benefit by being conducted in America, a larger sample size, a longer treatment interval, and a strict recording of symptoms.

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