RESEARCH ARTICLE

Efficacy of Ginger in Control of Chemotherapy Induced Nausea and Vomiting in Breast Cancer Patients Receiving Doxorubicin-Based Chemotherapy

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Abstract

Nausea and vomiting are among the most serious side effects of chemotherapy, in some cases leading to treatment interruption or chemotherapy dose reduction. Ginger has long been known as an antiemetic drug, used for conditions such as motion sickness, nausea-vomiting in pregnancy, and post-operation side effects. One hundred and fifty female patients with breast cancer entered this prospective study and were randomized to receive ginger (500 mg ginger powder, twice a day for 3 days) or placebo. One hundred and nineteen patients completed the study: 57 of them received ginger and 62 received ginger for the first 3 chemotherapy cycles. Mean age in all patients was 48.6 (25-79) years. After 1st chemotherapy, mean nausea in the ginger and control arms were 1.36 (±1.31) and 1.46 (±1.28) with no statistically significant difference. After the 2nd chemotherapy session, nausea score was slightly more in the ginger group (1.36 versus 1.32). After 3rd chemotherapy, mean nausea severity in control group was less than ginger group [1.37 (±1.14), versus 1.42 (±1.30)]. Considering all patients, nausea was slightly more severe in ginger arm. In ginger arm mean nausea score was 1.42 (±0.96) and in control arm it was 1.40 (±0.92). Mean vomiting scores after chemotherapy in ginger arm were 0.719 (±1.03), 0.68 (±1.00) and 0.77 (± 1.18). In control arm, mean vomiting was 0.983 (± 1.23), 1.03 (± 1.22) and 1.15 (±1.27). In all sessions, ginger decreased vomiting severity from 1.4 (±1.04) to 0.71 (±0.86). None of the differences were significant. In those patients who received the AC regimen, vomiting was less severe (0.64 ± 0.87) comparing to those who received placebo (1.13±1.12), which was statistically significant (p-Value <0.05). Further and larger studies are needed to draw conclusions.

Keywords: Chemotherapy - nausea - vomiting - ginger

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Introduction

Despite advances in chemotherapy agents and antiemetic drugs, chemotherapy induced nausea and vomiting (CINV), is one of the worst side effect of cancer treatment (Palatty et al., 2013; Marx et al., 2014). In addition to having a devastating experience, CINV may cause malnourishment and consequently affect the immune system, performance status, electrolyte imbalance, and quality of life. CINV may also lead to treatment interruption or dose reduction and consequently lead to reduction in cure rate (Shankar et al., 2015; Navari and Aapro, 2016). Despite the decrease in CINV by using multiple classes of antiemeting agents, CINV occurs in 60-80% of chemotherapy patients (Ryan et al., 2012; Wang et al., 2014b). Common antiemetic agents are 5-HT3 receptor antagonists, NK1 receptor antagonist, steroids, dopamine antagonists, cannabinoids, and antihistamines (Palatty et al., 2013). These Antiemetic agents may have significant side effects (Palatty et al., 2013; Wang et al., 2014a; Wang et al., 2014b).

Ginger has been known as an antiemetic drug for years. It is used in several conditions such as; motion sickness, nausea-vomiting (N/V) in pregnancy, and post operation N/V (Panahi et al., 2012). In animal studies, it was shown that Ginger may have antiemetic effects via 5-HT3 receptor antagonist activity (Sharma and Gupta, 1998). This study was conducted to evaluate the effect of Ginger powder on N/V after chemotherapy in breast cancer patients.

Materials and Methods

CThis is a phase II-III clinical trial that was conducted

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in Namazi Hospital affiliated with Shiraz University of Medical Sciences, Shiraz, Iran. Study started on Jan 2013 and finished on Dec 2014. One hundred and fifty newly diagnosed breast cancer patients who were going to receive doxorubicin based chemotherapy were included in the study. Chemotherapy regimens were AC (doxorubicin60 mg/m^2 +cyclophosphamid 600 mg/m2), CAF (cyclophosphamide 500mg/m^2 + doxorubicin 50mg/m^2 + 5-Fluorouracil 500mg/m^2), and TAC (docetaxel 75mg/m^2+ doxorubicin 50mg/m^2+ cyclophosphamide 500mg/m^2). All the participants were given treatment every 3 weeks. Those who received AC, continued their treatment after 4th cycle by Taxane (Docetaxel or Paclitaxel). Premedication before each chemotherapy injection consisted of; Dexamethasone 16 mg intravenous (IV), Aprepitant 125mg orally and Granisetron 3 mg IV. Dexamethasone 8 mg orally and aprepitant 80 mg orally continued for the following 2 days.

Patients were randomly selected in to 2 groups and both patients and oncologists were unaware of capsules content. Seventy five patients received Ginger capsules and the other 75 patients received placebo. Inclusion criteria were pathologically diagnosed breast cancer, receiving AC, CAF or TAC chemotherapy regimen, receiving at least 3 chemotherapy cycles. Exclusion criteria were history of previous malignancy or chemotherapy, history of other systemic diseases, metastatic condition or receiving other antiemetic drugs. Before commence of treatment and before each chemotherapy administration, history and complete physical examination was performed for all patients. Patients had no known sensitivity to herbal drugs, no coagulopathy. Liver function tests, renal function tests and complete blood count were done 1-2 days prior to each chemotherapy injection.

Ginger and placebo capsules were in the same shape and color. Both capsules were made by Goldaru Co, Isfahan, Iran and contained 250 mg Ginger powder or starch. Capsules were put in similar packages and were named A or B. Randomization of patients and treatment delivery was carried out by a radiation Oncology resident. Patients and their oncologists were unaware of the capsules content. Patients were asked to eat 2 capsules every 12 hours for 3 days and record the episodes of vomiting and nausea severity. Then raw data were categorized according to common terminology criteria for adverse events version 4 (Table 1).

Statistical analyses were made by SPSS and Chi-square test, Independent T-test and Mann-Whitney test were used. P-value of less than 0.05 was considered significant.

Results

One hundred and fifty patients entered the study and 450 chemotherapy cycles were performed. Mean age in all patients was 48.56 (25-79) years. Eighty five patients received AC, 37 patients received CAF and 28 patients received TAC. In Ginger group 41, 19 and 15 patients received AC, CAF and TAC. In control group 44, 18 and 13 patients received AC, CAF and TAC. Patients were randomly assigned to 2 groups, Ginger group and control group.

When the study was finished, 31 patients were excluded from the study. None of these 31 patients had shown negative reaction to Ginger. Most of them had forgotten to record their discomfort status in some days. After each chemotherapy cycle, anyone who had not filled the forms was excluded from the study. No treatment (chemotherapy) interruption was observed. After the data collection, 119 patients had recorded their condition with accurate detail to be evaluated. In Ginger group, 57 patients filled the forms completely and in control group 62 patients filled the forms completely.

As shown in table 2, no statistically significant difference, in decrease of nausea and vomiting severity was reported between the 2 groups.

After 1st chemotherapy session, in Ginger group, 24 patients had no nausea and 6, 9 and 18 patients had grade 1, 2 and 3 nausea, respectively. In control group 22, 10, 9 and 21 patients had grade 0, 1, 2, and 3 nausea, respectively. Mean nausea in Ginger and control arms were 1.36(±1.31) and 1.46(±1.28) with no statistically significant differences.

After 2nd chemotherapy session, nausea score was slightly more in Ginger group (1.36 versus 1.32). Hence, this difference was not significant. Among those who received Ginger, 25 patients had no nausea. Four, 10 and 18 patients had grades between 1-3 nausea. The mean severity of nausea was 1.36(±1.33). In the control group 20, 18, 8 and 16 patients had grade between 0, 1, 2, and 3 nausea with a mean of 1.32(±1.18), respectively.

After 3rd chemotherapy session, in the control group, 20, 12, 17 and 13 patients had grade 0-3 nausea. Those who received Ginger 23, 5, 11 and 18 patients had grades 0-3 nausea. Mean nausea severity in control group was less than Ginger group [1.37(±1.14), versus 1.42(±1.30)]. But the difference was not statistically significant.

With regards to interaction of chemotherapy and Ginger, effect of this intervention was analyzed in patients who had received AC, CAF and TAC, separately. Mean nausea grade in control group in AC, CAF and TAC subgroups were, 1.36 (±0.87), 1.41 (±1.08), and 1.50 (±0.91), respectively. In Ginger group these grades were 1.43(±0.96), 1.21(±0.92), and 1.67(± 0.99). No significant difference was observed.

Considering all patients, nausea was slightly more severe in Ginger arm. In Ginger arm mean nausea score was 1.42 (±0.96) and in control arm it was 1.40 (±0.92). Ginger decreased nausea in AC subgroup and, on the other hand, it was increased in CAF and TAC subgroups. But none of these differences were significant.

After 1st chemotherapy session Ginger reduced vomiting severity from 0.983 (±1.23) to 0.719 (±1.03). In Ginger arm, 35 patients did not vomit but 8, 9 and 5 patients had grades 1 to 3 vomiting, respectively. In the other arm 34, 8, 7 and 13 patients had grades 0-3 vomiting. These differences were not significant.

After 2nd and 3rd chemotherapy sessions, as was seen in 1st session, Ginger decreased vomiting severity from 1.03(±1.22) to 0.68(±1.00). After 3rd session vomiting severity decreased from 1.15(±1.27) to 0.77(± 1.18). In Ginger arm 35, 10, 7, and 5 patients and in control arm

Table 1. Nausea and Vomiting Grading. Total Parenteral Nutrition (TPN)

Adverse event	1	2	3
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN or hospitalization indicated
Vomiting	1-2 episodes (separated by 5 minutes) in 24 hours	3-5 episodes (separated by 5 minutes) in 24 hours	>5 episodes (separated by 5 minutes) in 24 hours; tube feeding, TPN or hospitalization indicated

Table 2. Frequency and grade of CINV among Ginger and control groups

		Cycle 1	Cycle 2	Cycle 3
Nausea in control group	Grade 0	22	20	20
	Grade 1	10	18	12
	Grade 2	9	8	17
	Grade 3	21	16	13
Nausea in ginger group	Grade 0	24	25	23
	Grade 1	6	4	5
	Grade 2	9	10	11
	Grade 3	18	18	18
Vomiting in control group	Grade 0	34	32	32
	Grade 1	8	9	3
	Grade 2	7	8	13
	Grade 3	13	13	14
Vomiting in ginger group	Grade 0	35	35	38
	Grade 1	8	10	3
	Grade 2	9	7	7

32, 9, 8, and 13 patients had grades 0-3 vomiting after 2nd session. After 3rd cycle, 32, 3, 13, and 14 patients had grades 0-3 vomiting severity in control arm and 38, 3 7 and 9 patients had grades 0-3 vomiting. None of these differences were significant. This difference was also not significant.

In all sessions, Ginger decreased vomiting severity from 1.4 (±1.04) to 0.71 (±0.86). In CAF subgroup, Ginger decreased vomiting severity; however, in TAC subgroup Ginger increased vomiting severity. None of the changes were statistically significant.

I AC subgroup those who received Ginger, vomiting was less severe (0.64 ± 0.87) comparing to those who received placebo (1.13±1.12), which was statistically significant (p-value <0.05).

Discussion

Ginger has been used as herbal remedy for hundreds of years as a medicine to treat gastrointestinal diseases. Its effects on nausea and vomiting were well known since antiquity. Its root (Rhizome) is used as a drug, in powder or extract forms (Ernst and Pittler, 2000; Chrubasik et al., 2005; Ryan et al., 2012; Marx et al., 2014). Ginger has been used as an antiemetic herbal drug in different circumstances such as post operation, pregnancy and post chemotherapy. The effects of Ginger has been widely studied in multiple trials (Chaiyakunapruk et al., 2006; Weimer et al., 2012) . It was shown that Ginger is an effective remedy in this setting. Ginger has anti-nausea and anti-vomiting effects via its central and gastrointestinal effects (Chaiyakunapruk et al., 2006).

Effective components are thought to be shogaols, gingerols, zingiberene, zingerone, and paradol. The main mechanisms of Ginger properties are unknown. It may act via substance P, 5-HT3 and NK-1 receptors in a dose dependent manner (Palatty et al., 2013; Marx et al., 2014). Anti emetic and motility effects of Ginger is also mediated via Cholinergic M3 receptors (Giacosa et al., 2015). Animal trial studies have shown that Ginger increases gastric emptying and intestinal motility (Giacosa et al., 2015).

Studies have shown that Ginger is a safe drug and has no severe side effects. A 2.5 gr/Kg of Ginger extract (solvent 80% ethanol) produced mild diarrhea in 20% of rats. In sited articles we found no adverse reaction to Ginger (Chrubasik et al., 2005). Adherence rate in different studies was 75-90%. In our study adherence rate in Ginger and control arm was 76% and 82% (Marx et al., 2013).

Sontakke et al., in a cross over study on 50 patients, who received combination chemotherapy (cyclophosphamide based) compared Ginger, metoclopramide and ondansetrone. They administered 1 gr of Ginger before and 1 gr 6 hours after chemotherapy. Interestingly in this study, patients were hospitalized and episode of nausea and vomiting were recorded. Ondansetrone was significantly better than the other two agents. Ginger was as strong as metoclopramide in controlling both nausea and vomiting (Sontakke et al., 2003). In their study, patients received only Ginger or metoclopramide or ondansetron. Although this study was a well designed, cross over study, the antiemetic regimen that was used is not routine nowadays.

Ryan et al. (2012) in a large multicentre study on 576 patients, during a 6.5 years period, reported a good acute phase nausea control. They used different doses of Ginger (0.5-1.5 gr daily), for 6 days. They used Ginger liquid extract, equivalent to 250 mg of Ginger powder. In their study most patients were female (93%) and 74% had breast cancer, however, chemotherapy agents were not mentioned. Early nausea was significantly reduced on day one. Hence, quality of life and vomiting and late nausea were not reduced (Ryan et al., 2012). In our study early N/V were not reduced in Ginger arm as well.

Fahimi et al., in a prospective study on 50 patients administered Ginger and cisplatin, they administered 1 gr of Ginger for 3 days but it was only for one course and in the next course they were switched to the other arm. From 50 patients, 36 of them finished the study. Neither early nor delayed N/V was changed in Ginger arm. One patient developed rash, pruritis and gastrointestinal discomfort with Ginger (Fahimi et al., 2011). In our study no Ginger related side effects were reported.

Interaction of chemotherapy with Ginger has not been fully studied. In our study those who received AC had less vomiting than the control arm. Ginger may be more effective in some chemotherapy regimens.

Ginger has also been used in children. Pillai et al., study on 31 children between 8-21 years of age with osteosarcoma who were receiving Cispltin and Doxorubicin. In this study, chemotherapy cycles were randomized, rather than patients. Patients who weighted between 20-40 Kg received 1 gram Ginger and those who weighted between 40-60 Kg received 2 gram of Ginger or placebo for 3 days. No side effect with Ginger was reported. Moderate to severe N/V both in acute and delayed phase were significantly reduced by Ginger. In addition, mild N/V were also significantly less frequent in Ginger arm (Pillai et al., 2011).

Manusirivithaya et al., in a randomized cross over study on 43 patients with gynecological cancer compared 5 days of 1 gram Ginger with placebo. Chemotherapy was cisplatin based and anti emetic mediations were metoclopramided, dexametasone and lorazepam. No difference between placebo and Ginger, in acute and delayed phase, was observed. In this study no side effect with Ginger was reported (Manusirivithaya et al., 2004).

Panahi et al., on 78 patients with breast cancer compared 1.5 gram of Ginger daily for 5 days with placebo. Initially 100 patients were entered in that study. It's worth mentioning that none of the 22 patients who left the study had showed any adverse reaction to Ginger. Patients were treated by Docetaxel, Epirubicin and Cyclophosphamide. Antiemetic regimen in this study was granistrron and dexametasone and 1st dose of Ginger was given 30 minutes after chemotherapy session. Ginger significantly decreased nausea during the 1st day , however it was not beneficial compared to conventional antiemetic therapy during the rest of the study (Panahi et al., 2012).

In conclusion, Ginger is a safe herbal medication but its effects on CINV are not well defined. Further studied are needed in order to draw a conclusion. In further studies, longer period of Ginger consumption, before and after chemotherapy, and using Ginger during the whole treatment course may be helpful.

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