



CHEMOTHERAPY INDUCED NAUSEA AND VOMITING; EFFICACY OF ADDING GINGER TO STANDARD THERAPY AS PROPHYLAXIS FOR CHEMOTHERAPY INDUCED NAUSEA AND VOMITING (CINV) IN CANCER PATIENTS.

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ABSTRACT... Background: Ginger has long been used as an antiemetic herb in various systems for traditional medicine. However, lack of data on its utility in preventing chemotherapy induced vomiting prevents us from reaching any definite statement. **Objectives:** To determine the effect of prophylactic use of ginger in decreasing the delayed chemotherapy induced vomiting, when added as an add on therapy to the standard antiemetic treatment in patients receiving highly emetogenic chemotherapy. **Study Design:** Randomized control trial. **Setting:** Department of Medical Oncology, Jinnah Hospital Lahore. **Period:** July 2014 and January 2016. **Materials and Methods:** A total of 90 patients were selected and randomly allocated into two groups, A and B, having 45 patients each. Patients in both groups received highly emetogenic chemotherapy regimens. For prophylaxis of CINV, Group A received olanzapine based standard antiemetic regimen and cap ginger 500 mg per oral TID 3 days prior to chemotherapy and 3 days after chemotherapy and Group B received olanzapine based standard antiemetic regimen only. Observation for frequency and grade of delayed chemotherapy induced vomiting in all cases was done at day 8 of chemotherapy. **Results:** The mean age of the patients in group A (intervention group) is 44.5 ± 12.8 years and that in group B (standard group) is 41.4 ± 13.9 years. 29 (64.4%) patients in the intervention group had no vomiting at all as compared to the 19 (42.2%) patients in standard group. Mild/Grade 1 vomiting was experienced in 6 (13.3%) patients in the intervention group as compared to 9 (20.0%) patients in the standard arm. There was also a significant reduction in moderate/grade 2 vomiting in intervention arm 7 patients (15.5%) as compared to 11 patients (24.4%) in control arm. There was also significant reduction in the severe vomiting that is grade 3 and 4 in group A with the use of ginger capsules grade 3 vomiting was observed in only 6.6% versus 15.5% patients, while none had grade 4 vomiting in group A compared to one patient (2.2%) in group B. **Conclusion:** Significant decrease in delayed chemotherapy induced vomiting was achieved in patients who were treated with standard antiemetic regimen plus ginger than those treated with standard antiemetic regimen alone, in patients receiving highly emetogenic chemotherapy. So the addition of ginger to standard antiemetic regimens is a safe, less expensive and effective additional treatment option.

Key words: Frequency, CINV, Ginger, Chemotherapy.

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INTRODUCTION

Chemotherapy induced nausea and vomiting (CINV) is commonly experienced by the cancer patients being treated with chemotherapy. It continues to affect a significant proportion of patients despite the widespread use of a variety of anti-emetic regimens. Certain chemotherapeutic agents like Cisplatin, Carmustine, Dacarbazine, Mechlorethamine, Streptozocin and combination regimens like Anthracycline and Cyclophosphamide which are particularly used in

breast cancer and soft tissue sarcoma patients are considered highly emetogenic and the risk of CINV in such patients is more than 90%, while other single agent Carboplatin, Doxorubicin, Daunorubicin, Ifosfamide, Imatinib, Methotrexate, Paclitaxel are classified as moderate to low risk for CINV.^{1,2} Chemotherapy induced nausea and vomiting (CINV) can be acute, delayed or anticipatory. Acute CINV occurs within 24 hours of beginning the chemotherapy whereas Delayed CINV occurs after 24 hours, and Anticipatory

CINV is the N&V that occurs as an accustomed response to the chemotherapy associated stimuli in subsequent cycles e.g sight or smell of the treatment room, because the patient has experienced significant CINV in the past.³

The standard regimen for prophylaxis against CINV caused by highly emetogenic chemotherapeutic agents includes 5-HT₃ receptor antagonist, dexamethasone, and metoclopramide, as per guidelines of Multinational Association of Supportive Care in Cancer (MASCC)/European Society for Medical Oncology (ESMO). However, the use of these drugs is effective against acute CINV only, and it has shown poor control of the delayed and anticipatory nausea and vomiting.^{2,4-6} Therefore, this area needs to be explored further addition of drugs like antipsychotics (olanzapine) or NK1 receptor antagonist aprepitant, fosaprepitant, netupitant (with palonosetron or rolapitant) to the standard regimen, can be done in this regard to provide a better control.^{7,8} Also, agents like benzodiazepines, cannabinoids, haloperidol etc has been used to control breakthrough vomiting.⁹⁻¹² But in a developing countries like Pakistan, all these drugs are either not available or are very costly and a common man can not afford it. So they are not routinely prescribed as prophylaxis against CINV. Literature shows that ginger (*Zingiber officinale*), an inexpensive and naturally found root, has antiemetic qualities that can effectively reduce CINV.¹³⁻¹⁶

The pathophysiology of acute CINV involves the stimulation of 5-HT and 5-HT₃ receptors in the gastrointestinal tract and the delayed CINV is mediated by the central activation of NK1 receptors (by substance P) Blocking these receptors from activation should prevent the emesis.¹⁷⁻¹⁹ It has constituents like gingerols, shogaols, galanolactone and diterpenoid, that provide the anti-nausea and antiemetic property and utilized in the treatment of postoperative and pregnancy induced nausea and vomiting, and for motion sickness in traditional medicine.²⁰⁻²⁴ Pillai et al²⁵ done a study in children and young adults, on a combination of Cisplatin and doxorubicin for bone sarcomas significantly reduced both acute

and chronic CINV with the addition of ginger root powder capsules (93.3% vs 55.6% $P = 0.003$, 73.3% vs 25.9% with $P < 0.001$ respectively.²⁵ Ginger is a natural and inexpensive product, widely available in Pakistan. While the newer drugs in this regard remain largely unavailable here, in order to establish the efficacy of ginger in our population as prophylaxis for CINV we conducted this randomized controlled trial receiving highly emetogenic chemotherapy.

MATERIALS AND METHODS

This randomized control trial was conducted at department of Medical Oncology, Jinnah Hospital Lahore, after approval from the departmental ethical review committee. The study took place between July 2014 and January 2016.

A total of 90 Patients were included in the study. Patients were enrolled only if they were (i) aged between 18 to 60 years, (ii) receiving highly emetogenic chemotherapy regimens and (iii) having cardiac, renal and liver function within in normal limits on Echocardiography and blood test results. However, pregnant patients and/or those having brain metastasis, having signs and symptoms of gastrointestinal obstruction were excluded from the study.

The selected cases were then allocated into two groups (A & B) by using random numbers table. Both groups had 45 patients each. Group A, the Intervention arm received Olanzapine based standard antiemetic regimen plus capsule Ginger 500 mg per oral three times a day, 3 days prior to chemotherapy continued until after 3 days of chemotherapy. The control arm, i.e Group B received Olanzapine based standard antiemetic regimen only. Frequency of delayed chemotherapy induced vomiting in terms of grade of vomiting (as per CTCAE criteria version 4.03, that is; single episode in 24 hours: grade 1, 2-5 episodes in 24 hours: grade 2, 6 or more episodes in 24 hours: grade 3, vomiting with life threatening consequences: grade 4 and vomiting causing death: grade 5) were recorded during seven days after the completion of chemotherapy, because of the fact that delayed chemotherapy induced vomiting occurs after 24

hours of chemotherapy and usually persists for 48 to 72 hours and may even prolong up to one week.²⁶ A specially designed proforma was used for collecting relevant data. Data was analysed using SPSS version 20.

RESULTS

The mean age of the patients in group A is 46.4±10.6 years and in group B is 44.2±11.6 years. There were 60 (66.7%) males and 30 (33.33%) females. A majority 24 (26.7%) of patients had head and neck cancers (including nasopharyngeal, laryngeal, oral cavity and salivary gland tumors) and breast cancer 15 (16.7%) (Table-I). The distribution of patients by chemotherapy regimens received, shows 54 (60.0%) patients were administered platinum based regimens, 21 (23.3%) patients received anthracyclins based regimens, and 15 (16.7%) patients received DTIC based regimens (Figure-1). Significantly higher percentage of patients in the intervention arm (group A) compared to the standard therapy (Group B) did not have even a single episode of vomiting (64.4% versus 37.7%, p value 0.006). Mild vomiting was experienced in 6 (13.3%) patients in the intervention group compared to 7 (15.5%) patients in the standard arm. Almost double the number of patients in the standard arm had grade 2 vomiting compared with the intervention arm 15.5% vs 28.9% in group A and Group B respectively. There was also significant reduction in the severe vomiting that is grade 3 and 4 in group A with the use of ginger capsules as grade 3 vomiting was observed in only 6.6% versus 15.5% patients, while none had grade 4 vomiting in group A compared to one patient (2.2%) in group B (Figure-2).

DISCUSSION

For thousands of years, ginger (Zingiber officinale) had been used in traditional medicine to prevent and treat nausea. However, its use with chemotherapy has not yet been properly established. The characteristic odour and flavour of ginger is caused by a mixture of zingerone, 6-shogaol, 6-gingerol and galanolactone and volatile oils. Gingerols increase the motility of gastrointestinal tract and accelerate gastric emptying.^{20,27}

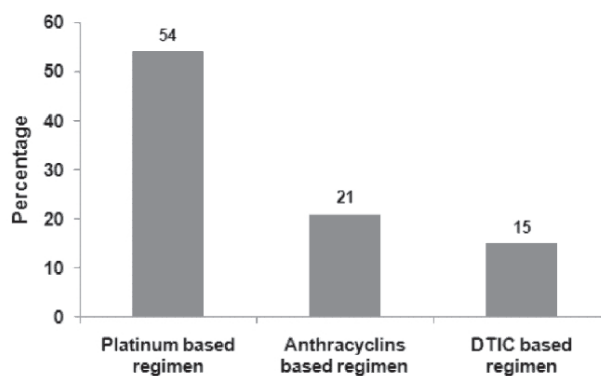


Figure-1. The distribution of patients by chemotherapy regimens received

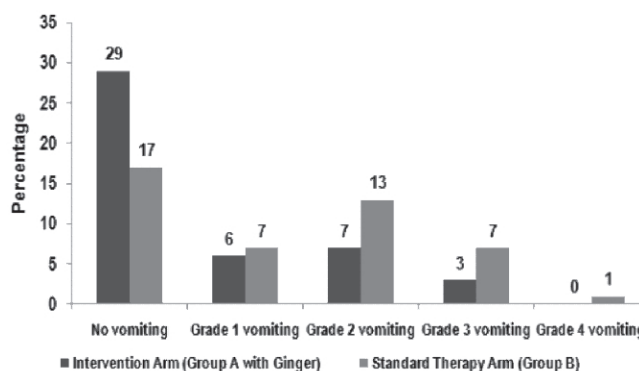


Figure-2. Distribution of patients by grade of vomiting in the two treatment groups

Characteristic	Intervention Arm (n=45)	Standard Arm (n=45)
Age	46.4±10.6	44.2±11.6
Sex		
Male	29 (64.4%)	31 (68.9%)
Female	16(35.6%)	14(31.1%)
Diagnosis		
Head & Neck Carcinoma	24 (26.7%)	
Breast Carcinoma	15 (16.7%)	
Genitourinary Carcinoma	12 (13.3%)	
Gynecological cancer	8 (8.9%)	
Soft tissue sarcoma	10 (11.1%)	
Hodgkins lymphoma	9(10.0%)	
Small Cell CA Lung	6 (6.7%)	
Anorectal Carcinoma	3 (3.3%)	
Malignant Melanoma	3 (3.3%)	

Table-I. Demographic distribution of patients

More than 90% of patients receiving highly emetogenic chemotherapy will have episodes of vomiting.^{28,29} HOWEVER, with standard antiemetic drugs, up to 70% patients receiving highly ematogenic chemotherapy may experience

CINV.³⁰ Our data is consistent with this study as more than 62% patients had some grade of vomiting with standard therapy, with almost half of the patients vomiting six or more times a day that is having grade 2 vomiting. Therefore there is not much difference in terms of prevalence of CINV with highly emetogenic therapy in our populations and international literature.

The results of the present study did respond significantly to the addition of ginger capsules and only 35.6% patients had vomiting after chemotherapy as compared to 62% patients in standard therapy arm. These results are quite encouraging in our population but another randomized and double-blind study, carried out in this regard in 2009, included 162 patients with previous history of CINV concluded that adding ginger to serotonin antagonist and/or aprepitant has no advantage in reducing the degree and frequency of acute or delayed CINV.³¹ Panahi et al³² reported that addition of ginger (1.5g/day) to standard prophylactic antiemetic regimen reduces the prevalence of nausea between 6 to 24 hours of chemotherapy (35.1% in ginger group vs 58.5% in control group with $P = 0.04$).³² This Iranian study results are more in line with our results showing almost similar difference and decrease in the CINV due to the addition of ginger in standard antiemetic therapy. Another study showed that ginger has no significant effect on acute CINV but carries an equal efficacy as metoclopramide in controlling delayed CINV.³³ Ansari et al³⁴ also reported that the use of ginger showed a reduction in the severity of vomiting, i.e. 0.64 ± 0.87 on a scale of 0 to 3, versus 1.13 ± 1.12 in placebo group (p -value < 0.05).³⁴ Therefore, both studies have similar results and support each other.

CONCLUSION

The addition of ginger to the standard antiemetic therapy in patients receiving highly emetogenic chemotherapy proved significantly effective in reducing the delayed chemotherapy induced vomiting of all grades particularly complete prevention of vomiting in a large number of patients and marked reduction of grade II and grade III (moderate to severe) vomiting as compared to control arm. There were no adverse

events seen with the use of ginger. Hence adding ginger to the currently used standard antiemetic regimens is a safe, less expensive and effective additional treatment option in patients receiving highly emetogenic chemotherapies.

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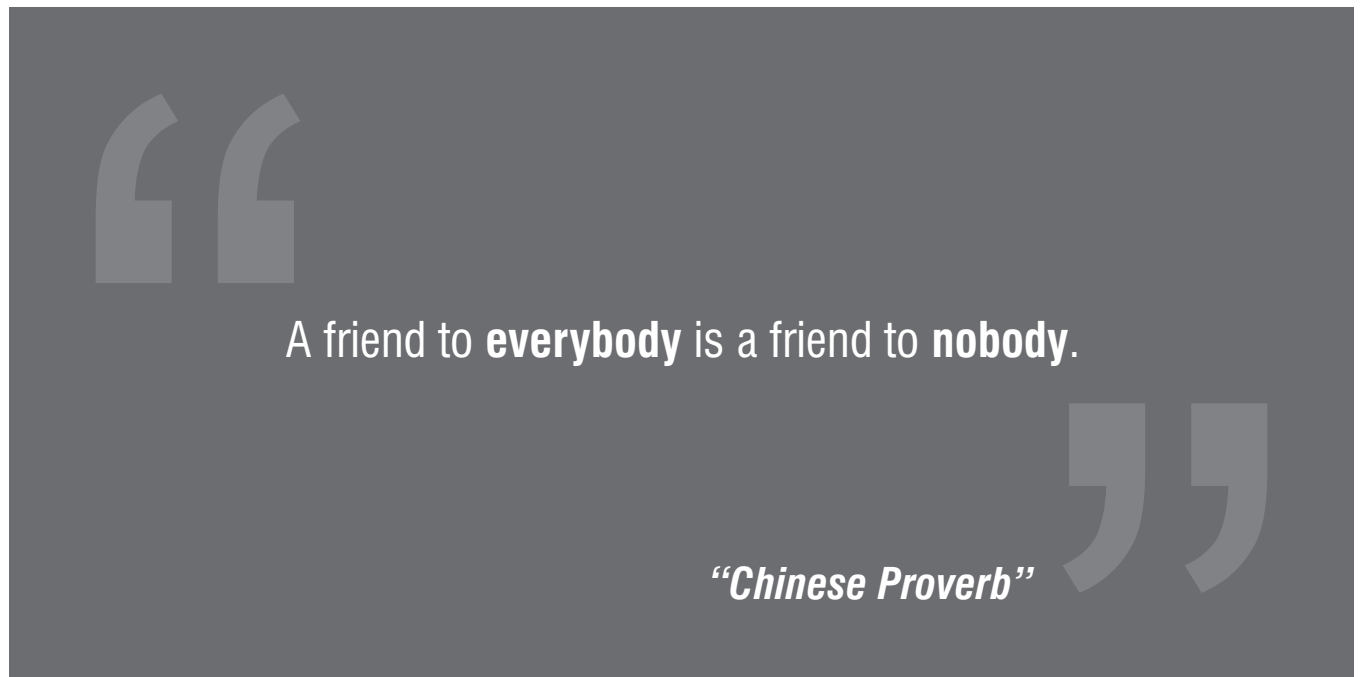
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2	M. Abbas khokhar	Data collection & writing of manuscript.	
3	Sadaf Ilyas	Statistical analysis	
4	Samina Qamar	Guidance in writing the manuscript.	