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Ginger Relief Chemotherapy Induced Nausea and Vomiting (CINV) in Children: A Randomized Clinical Trial

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Abstract

Background

One of the major adverse effects of chemotherapy is chemotherapy induced nausea and vomiting (CINV) which can obviously reduce patients' quality of life. Ginger (Zingiber officinale), an herbal supplement, has been used for centuries for gastrointestinal complaints. Although many surveys have been conducted to find the efficiency of ginger on CINV, its benefit has not been proven yet. We aimed to find ginger's efficiency on pediatric patients throughout their chemotherapy cycles.

Materials and Methods: This was a double-blinded, randomized, single institutional, placebo-controlled trial conducted at oncology ward in Aliasghar children's hospital, Tehran, Iran. The study took place between October 2017 and October 2018. We included 49 chemotherapy cycles, 25 cycles for treatment group and 24 cycles for placebo groups. Intervention group took encapsulated ginger which contained 240mg of powdered ginger (Nausophar), and control group took placebo. All patients took the study medication four times per day (every 6h), starting on the first day of chemotherapy until 24h after completion of chemotherapy. Frequency and severity of nausea and vomiting were measured by Edmonton's Symptom Assessment Scale (ESAS) from the first day of chemotherapy until 24h after completion of chemotherapy.

Results: The median age of all participants was 13 (IQR=8-14 year-old). Fourteen patients were male (28.6%), and 35 patients were female (71.4%). There were no significant differences in distribution of patients' characteristics in two groups. The frequency and severity of nausea and vomiting were significantly lower in ginger group ($p<0.05$).

Conclusion

According to our findings, ginger acts as an efficient antiemetic for pediatric patients. We recommend that ginger be prescribed as well as other antiemetics like Granisetron, with no loss of function.

Key Words: Cancer, Chemotherapy, Children, Ginger, Nausea, Vomiting.

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1- INTRODUCTION

Chemotherapy has had a significant role in the treatment of cancer for years. However, this cytotoxic treatment has varied adverse effects (1). One of the most common adverse effects is chemotherapy-induced nausea and vomiting (CINV) which has a negative influence on the quality of life and patients acknowledge it as one of the major adverse impacts of chemotherapy (2, 3). The mechanism of chemotherapy induced emesis has not been defined very well as yet, but investigations reckon it may happen due to neurotransmitters such as serotonin, dopamine and substance P in the gastrointestinal (GI) tract and the central nervous system (CNS) (4). On the other hand, studies have shown that the reason of vomiting is activation of neurotransmitter receptors located in the chemoreceptor trigger zone (CTZ), GI tract and vomiting center (VS) by chemotherapeutic agents (5).

CINV is categorized into 5 groups by time of happening (5): acute (it occurs in the first 24h after chemotherapy administration) (6), delay (it occurs more than 24h after chemotherapy administration), anticipatory (it occurs prior to chemotherapy because of a conditional response), breakthrough (it occurs up to 5 days after taking a prophylactic antiemetic agent or needs rescue) and refractory (it occurs after chemotherapy in situation that previous antiemetic prophylaxis or rescue in earlier cycles failed) (2, 5, 7, 8). Recent studies have demonstrated that CINV can be controlled by using a combination of a 5-HT3 receptor antagonists, corticosteroids, a neurokinin 1 (NK1) receptor antagonist and anti-anxiolytics (1, 5). It is important to mention that these anti-emetic agents have some adverse effects, for instance, Casopitant can induce neutropenia, alopecia and constipation (5). In spite of using a combination of antiemetic agents, nausea remains as a prominent problem for patients, conversely vomiting is better controlled (9). Ginger (Zingiber officinale) is an herbal supplement which has been taken for gastrointestinal complaints for centuries (10), and it is a traditional antiemetic agent (11). Also, the studies have shown that ginger has a therapeutic effect on motion sickness and migraine (12, 13), pregnancy induced nausea (14, 15), and postoperative nausea and vomiting (16). Moreover, two clinical trials found that ginger is as effective as metoclopramide in reducing CINV is similar to that ofmetoclopramide (17, 18). Studies have recognized that ginger's components (i.e., gingerols and shogaols) have inhibitory effect on 5-HT3 receptors (19, 20), and cholinergic M3 receptors (20). Nevertheless, the efficiency of ginger on CINV has not beenproven yet so its efficiency is still uncertain (1, 5, 9, 21-23). There is a lack of adequate evidence on the efficiency of ginger in controlling CINV in children. Hence, in this randomized clinical trial we tried to discover whether encapsulated ginger can relieve CINV in children who are on chemotherapy or not.

2- MATERIALS AND METHODS

2-1. Study design and ethics

This was a double-blinded, randomized, single institutional, placebo-controlled trial conducted at oncology ward in Aliasghar children's hospital, Tehran, Iran. Aliasghar hospital is a pediatric, university-affiliated, community inner-city hospital located in Tehran, Iran. The study took place between October 2017 and October 2018. The study protocol was approved by institutional ethics committee of Iran University of Medical Sciences (IR.IUMS.FMD.REC 1396.9511520002). Our RCT code is IRCT201710156396N2. All patients and their parents provided written informed consent prior to their participation in the study.

2-2. Participants

To be considered eligible, participants must be on chemotherapy and be at least 6 years-old with experience of CINV in previous cycles. In addition, they must not have had any evidence of gallstones and underlying coagulation disorders. Also, patients must not have taken any thrombolytic or heparin. Patients who encountered any coagulation disorders during trial or who refused to participate in trial were excluded.

2-3. Sample size, blinding, randomization

We included 49 chemotherapy cycles, 25 cycles for treatment group and 24 cycles for placebo groups. The cycle of chemotherapy was the unit of randomization and each chemotherapy cycle, using blocked randomization, was assigned in a 1:1 randomization procedure to one of two groups: treatment experimental group (receiving ginger powder capsules, Nausophar) or control group (receiving placebo). Both the placebo and the ginger capsules had their own code and not only all study participants but also all study personnel (such as investigator, outcome evaluators, and data analyzers) were unaware about the content of capsules. The placebo capsule was similar to the ginger capsule and it was prepared in the same factory and earmarked for the research team. The placebo was made of starch.

2-4. Study medication

The ginger and placebo capsules were manufactured by Know Tech Phar Corporation, Tehran, Iran. Each capsule of ginger contained 240 mg ginger powder and the dosage was chosen based on the manufacturer's recommendations and previous studies (24, 25). Placebo and ginger capsules were totally identical in appearance and flavor.

2-5. Procedure

All patients took the study medication four times per day (every 6 hours), starting on the first day of chemotherapy until 24h after completion of chemotherapy (intervention group took encapsulated ginger and control group took placebo). In addition, Granisetron was used as a routine and standard antiemetic during chemotherapy cycles in the same dose for all participants. In order to collect data about severity and frequency of nausea and vomiting, one blind data collector was responsible to fill the questionnaires in the presence of patients and their parents every night during the chemotherapy cycle from the first day until 24h after completion of chemotherapy. Questionnaires consisted of queries pertaining to frequency and severity of nausea and vomiting were measured by Edmonton's Symptom Assessment Scale (ESAS). This numerical assessment scale has a score of 1 to 10, based on patient's opinion about the severity; means that the symptom is absent and 10 means the worst possible severity (26). Persian version of this questionnaire was validated in previous study (27). Furthermore, participants' demographic profile was documented at the beginning of our study.

2-6. Statistical analysis

A professional blind statistician analyzed data using SPSS software (version 16.0). We reported data using means and standard deviation (SD) for continuous variables and counts and percentages for categorical variables. We utilize Kolmogorov Smirnov test to evaluate numerical variables' distribution. According to this test none of the numerical variables have normal distribution ($p<0.05$; K.S). So Mann-Whitney test was used to compare the medians in the two treatment groups. Chi-square was used to compare the qualitative variables. A P-value < 0.05 was considered statistically significant.

3- RESULT

3-1. Patient characteristics

Table.1 shows participants' baseline characteristics. No one was excluded from the study before initiation of treatment. Randomly, twenty-five patients (chemotherapy cycles) (51%) were assigned to receive ginger, while twenty-four of them (49%) were randomized to receive placebo. Regarding the distribution of patients' characteristics data, there are no significant differences in distributions: 14 patients were male (28.6%), and 35 patients were female (71.4%) and the sexual distribution was without significant difference between two groups. (p=0.47). Participants were 5 to 14 years old; the median age of all participants was 13 (IQR=8-14 year-old). In addition, the median age of patients in both control and treatment groups was 13 years-old without any significant statistical differences (p=0.934). These patients had been diagnosed with diverse kinds of malignancies: 24 cases (49%) had ALL, 17 cases (34.7%) had skeletal malignancies, 6 cases (12.2%) had PNET and 2 (4.1%) cases had neuroblastoma. In other words, 24 patients (49%) had ALL and 25 patients (51%) had other malignancies.

As the patients or their parents claimed, 23 patients (46.9%) had experienced severe nausea and 26 patients (53.1%) had experienced very severe nausea in the previous chemotherapy cycles. Furthermore, 26 participants (53.1%) had been receiving two or less doses of Granisetron daily and 23 participants (46.9%) had received more than two doses of this drug daily in the cycles prior to our trial. About medicinal cocktail (contain dexamethasone, diazepam and Granisetron), 6 participants (12.2%) declared they had been taking more than 2 cocktails daily, 40 participants (81.6%) had been taking 2 or less daily and 3 of them had not taken any cocktail in cycles before our trial. No significant differences were seen in the severity of nausea, taking Granisetron, and receiving drug cocktail in both groups according to Chi-square test ($p<0.05$).

3-2. Chemotherapy regimen

Incidence and severity of CINV is influenced by the chemotherapy regimen. **Table.1** demonstrated the regimen which patients took in our trial. As it has been shown 30 participants took MTX (methotrexate) as chemotherapy regimen in our trial, 14 patients in treatment group and 16 patients in placebo group. There was no significant difference between two groups (p=0.444).

Table-1: Basic Characteristics of Participants (Chemotherapy Cycles).

Characteristics	Total=49
Gender; n (%)	
Male	14 (28.6%)
Female	35 (71.4%)
Age in years; median (IQR)	
Ginger group	13(8-14)
Placebo group	13(8-14)
Cancer type; n (%)	
ALL	24 (49%)
Skeletal malignancies	17 (34.7%)
PNET	6 (12.2%)
Neuroblastoma	2 (4.1%)

Previous antiemetic	
Granisetron; n (%)	
>2 daily	23 (46.9%)
≤2 daily	26 (53.1%)
Cocktail; n (%)	
>2 daily	6 (12.3%)
≤2 daily	40 (81.6)
0	3 (6.1%)
Previous CINV; n (%)	
Severe	23 (46.9%)
Very severe	26 (53.1%)
Chemotherapy regimen; n (%)	
Methotrexate	30 (61.3%)
Ifosfamide+VP16	6 (12.2%)
Vincristine + Doxorubicin	3 (6.1%)
Cytarabine	3 (6.1%)
Doxorubicin	2 (4.1%)
Doxorubicin +Cisplatin	2 (4.1%)
Doxorubicin +Cisplatin +VP16+Cyclophsphamide	2 (4.1%)
Cisplatin	1 (2%)

IQR: Interquartile range; ALL: Acute lymphoblastic leukemia; PNET: Pancreatic neuroendocrine tumor; CINV: Chemotherapy-induced nausea and vomiting.

3-3. Frequency of nausea during trial

As we mentioned in method part, a blind data collector filled the questionnaires about nausea and vomiting starting on the first day of chemotherapy until 24 h after completion of chemotherapy cycle. Due to different chemotherapy regimens, cycle duration was varied. For instance, MTX regimen chemotherapy cycle took one day to be completed and then patients were followed for 1-day post-chemotherapy, it means participants who were on MTX regimen filled the questionnaire for 2 days. In fact, every patient was followed until 24 h after the cycle. In the first 2 days all 49 participants got involved and after that fewer patients were involved; according to their cycle duration. Totally, depending on the longest chemotherapy cycles in our trial, we followed participants up to seven days. **Table.2** demonstrates the frequency of nausea; as it is clear the prevalence of nausea in the intervention group was lower than in the placebo group meaningfully ($p < 0.05$).

Table-2: The comparison of frequency of nausea in intervention and placebo group.

Frequency of nausea	Placebo (n=24)	Ginger (n=25)	P-value
1st day	4 (3.25-4)	0 (0-0.5)	0.001
2nd day	3 (3-3)	0 (0-1)	0.002
3rd day	4 (3-4)	0 (0-1)	0.008
4th day	4 (3-4)	0 (0-1)	0.009
5th day	3 (3-3)	0 (0-0.75)	0.029
6th day	4 (4-4)	0	0.029
7th day	0	0	-

Data are presented as median (IQR). IQR: Interquartile range.

3-4. Severity of nausea during the trial

We measured severity of nausea by Edmonton's Symptom Assessment Scale (ESAS). According to **Table 3**, from day 1 until day 5 the nausea severity score was lower in the ginger group substantially ($p<0.05$), however, in the 6th day there was no significant difference ($p=0.343$).

3-5. Frequency of vomiting during the trial

As well as the frequency of nausea, the frequency of vomiting was significantly lower in ginger group in all days ($p<0.05$) (**Table.4**).

3-6. Taking Granisetron or medicinal cocktail

During the trial all participants received granisetron as a standard antiemetic in equal doses. Placebo group took granisetron significantly more than ginger group ($p<0.001$). Although drug cocktail is one of the routine antiemetics used in our oncology ward throughout chemotherapy cycles, no participants in ginger group needed it as an antiemetic.

3-7. Adverse events

There were no study-related adverse effects of ginger in our study.

Table-3: The comparison of nausea severity in intervention and placebo group.

Severity of nausea depending on ESAS	Placebo, (n=24)	Ginger, (n=25)	P-value
1st day	6 (6-7)	0 (0-2)	0.001
2nd day	4.5 (3-6)	0 (0-3)	0.001
3rd day	9 (7-9)	0 (0-3)	0.001
4th day	4 (4-4)	0 (0-3)	0.004
5th day	6 (6-6)	0 (0-2.25)	0.029
6th day	2 (2-2)	0 (0-2.35)	0.343
7th day	--	--	--

Data are presented as median (IQR). IQR: Interquartile range; ESAS: Edmonton Symptom Assessment System.

Table-4: The comparison of frequency of vomiting in intervention versus placebo group.

Frequency of vomiting	Placebo (n=24)	Ginger (n=25)	P-value
1st day	2 (1-2)	0 (0-0)	0.001
2nd day	1 (1-1.75)	0 (0-0)	0.002
3rd day	3 (1-3)	0 (0-1)	0.008
4th day	2 (1-2)	0	0.009
5th day	2 (2-2)	0	0.029
6th day	1 (1-1)	0	0.029
7th day	0	0	-

Data are presented as median (IQR). IQR: Interquartile range.

4- DISCUSSION

In this study we aimed to discover whether encapsulated ginger can relieve CINV in children who are on chemotherapy or not. The prevalence of nausea in the ginger group was lower than in the placebo group meaningfully. Also, the severity score of nausea during day 1 until day was lower in the ginger group too. As well as the frequency of nausea, the frequency of vomiting was significantly lower in ginger group in all days and there were no study-related adverse effects of ginger in our study. Until now, many surveys have been

conducted to discover ginger's efficiency on CINV. But the results were inconsistent, some of these studies have supported ginger's efficiency and some of them have not. These conflicts relate to many factors like diverse patients' characteristics, chemotherapy regimens, methods and ginger formulation and doses. For instance, Xiangfeng et al. worked on patients with lung cancer receiving Cisplatin-based regimen and they found no statically significant efficiency of ginger ($p > 0.05$) (28). Likewise, Thamlikitkul et al., did a research on population who suffered from breast cancer receiving adriamycin–cyclophosphamide regimen, they did not demonstrate any efficiency of ginger as well (29).

On the other hand, a meta-analysis of 10 RCT announced that ginger can be used as an adequate antiemetic to control CINV (30). Konmun et al., did a trial in solid tumor patients receiving moderate to highly emetogenic chemotherapy and demonstrated ginger as an acceptable antiemetic agent (31). Some studies counted extra benefits of ginger like decreasing fatigue and non-GI events besides an antiemetic effect throughout chemotherapy (32). Unfortunately, few studies have been done on the pediatric oncology patients. In this regard, involving children who suffer from CINV is this present study's most striking feature.

In our trial ginger reduced CINV in the pediatric patients. Hence, we believe it can be prescribed as an appropriate antiemetic throughout chemotherapy cycles in hospitals. Also, patients' quality of life will improve if CINV can be controlled as Ryan et al. declared (24). According to the previous studies, 6-gingerol and shogaol are bioactive ingredients of ginger (10, 29), and 0.5–1 g/day of 6-gingerol is sufficient to control acute nausea effectively when higher dosage does not have any additional effect (24). Despite both ginger and ondansetron being antagonists of 5-HT3 receptors (29), there is no contrariety to use them together, as Mandal et al., showed the benefit of using ginger and ondansetron together to prevent post-operative nausea and vomiting is more than using ondansetron alone (33). A recent study suggested that it might be more effective if patients use ginger continuously, in other words, ginger will be more efficacious in chronic use (31). Danwilai et al. explained that when patients use ginger continuously the oxidative stress will reduce and antioxidant activity will increase (34). Although herbal medications like ginger can have some drug interactions, researchers have not found many known drug interactions for ginger (12). Some adverse effects for ginger are demonstrated by previous trials like heartburn, diarrhea, dizziness and allergic reactions (24, 35).

None of these adverse effects were observed in our study. In addition, Nurtjahja Tjendraputra et al. declared that patients with coagulation disorders or patients who take anticoagulants are at risk for bleeding because there is a theory that ginger can inhibit platelet aggregation (36). Furthermore, previous study documented that the prevalence of nausea increased when ginger was co-administered with aprepitant (32). Zick et al., maintained that possibly increasing gastric emptying time and bowel motility and then decreasing the absorption of aprepitant lead to decline in antiemetic effect of aprepitant, thus this process can increase prevalence of nausea (32).

4-1. Study Limitations

Being a single institute survey which is based on a small population is a substantial limitation of our study. Our result would have been more reliable if we had involved more pediatric patients. Besides, difficulty in blinding was another limitation. Placebo and ginger were the same in shape and flavor, though it is likely they could be distinguished by their smell.

5- CONCLUSION

In conclusion, according to our study ginger can reduce severity and prevalence of CINV in children. So we recommend that ginger can be used as an efficient antiemetic for pediatric patients. We suggest that it be prescribed as well as other antiemetics like Granisetron.

6- CONFLICT OF INTEREST: None.

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