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Anti-Emetic Effect of Ginger Powder Versus Placebo as an Add-On Therapy in Children and Young Adults Receiving High Emetogenic Chemotherapy

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Purpose. Chemotherapy-induced nausea and vomiting (CINV) are major adverse effects of chemotherapy. Ginger has been used in postoperative and pregnancy-induced nausea and vomiting. Data on its utility in reducing CINV in children and young adults are lacking. ***Patients and Methods.*** Sixty chemotherapy cycles of cisplatin/doxorubicin in bone sarcoma patients were randomized to ginger root powder capsules or placebo capsules as an additional antiemetic to ondensetron and dexamethasone in a double-blind design. Acute CINV was defined as nausea and vomiting occurring within 24 hr of start of chemotherapy (days 1–4) and delayed CINV as that occurring after 24 hr of completion of chemotherapy (days 5–10). CINV was evaluated as per Edmonton's Symptom Assessment Scale and National Cancer Institute criteria respectively. ***Results.*** Acute moderate to severe nausea was observed in 28/30 (93.3%) cycles in control group as compared to 15/27 (55.6%) cycles in experimental group ($P = 0.003$). Acute moderate to severe vomiting was significantly more in the control group compared to the experimental group [23/30 (76.7%) vs. 9/27 (33.33%) respectively ($P = 0.002$)]. Delayed moderate to severe nausea was observed in 22/30 (73.3%) cycles in the control group as compared to 7/27 (25.9%) in the experimental group ($P < 0.001$). Delayed moderate to severe vomiting was significantly more in the control group compared to the experimental group [14/30 (46.67%) vs. 4/27 (14.81%) ($P = 0.022$)]. ***Conclusion.*** Ginger root powder was effective in reducing severity of acute and delayed CINV as additional therapy to ondensetron and dexamethasone in patients receiving high emetogenic chemotherapy (ClinicalTrials.gov identifier: NCT00940368). Pediatr Blood Cancer 2011;56:234–238.

Key words: chemotherapy; children; cisplatin; ginger; nausea; oncology; vomiting; young adults

INTRODUCTION

Chemotherapy induced nausea and vomiting (CINV) are two distressing toxicities of cancer treatment [1,2]. With certain chemotherapeutic agents such as cisplatin and doxorubicin, the incidence of CINV may be more than 90% depending on dosage and administration. Even with moderately emetogenic chemotherapeutic agents such as cyclophosphamide or carboplatin, CINV can range from 30% to 90% in patients not receiving anti-emetic medications [1,3].

Ginger (Zingiber officinale), a commonly used herbal supplement, is often consumed for culinary purposes. It is also found to be effective in reducing the severity of motion sickness and migraine [2,4]. Ginger has been shown to be effective for pregnancy-induced and postoperative nausea and vomiting [5–8]. There is limited information regarding its use as an anti-emetic in CINV among adults. Ryan et al. [9] have recently shown that ginger supplementation at a dose of 0.5–1 g/day significantly reduces nausea in adults during the first day of chemotherapy. However, there are no data regarding the anti-emetic efficacy of ginger in children and young adults receiving high emetogenic chemotherapy. Thus, we did a study to evaluate the efficacy of ginger powder in reducing CINV in children and young adults. Our hypothesis was that ginger powder is effective in reducing the incidence and severity of acute and delayed CINV in children and young adults.

PATIENTS AND METHODS

Study Design

This was a prospective, double-blind, randomized single institutional study conducted at our cancer center from June 2009 to December 2009 (ClinicalTrials.gov identifier: NCT00940368). The study protocol was approved by institutional ethics committee. Written informed consent was obtained from all patients and their parents or guardians according to institutional policies.

Patients

Children and young adults (8–21 years) with newly diagnosed bone sarcomas undergoing chemotherapy with high emetogenic potential, specifically a combination of cisplatin 40 mg/m^2/day and doxorubicin 25 mg/m^2/day for 3 days, were eligible for the study. Ondansetron and dexamethasone were used as standard antiemetics (4–8 mg) intravenously for first 3 days of chemotherapy. All patients received tablets of these antiemetics daily in the night during the first 3 days of chemotherapy and then three times daily for the next 2 days after completion of chemotherapy. Children and young adults with weight $\leq$20 kg or $\geq$60 kg, those receiving radiotherapy and patients additionally receiving aprepitant with the standard antiemetics were excluded.

Study Treatment

Chemotherapy cycles in subjects which met the eligibility criteria were randomly assigned using computer generated random numbers to one of the two groups: one group received ginger root powder capsules and the other group received placebo (starch powder) capsules from days 1 to 3 of the chemotherapy cycle. The unit of randomization was the cycle of chemotherapy, and all the

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Conflict of interest: Nothing to declare.

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TABLE I. Plan for Administration of Capsules Based on Weight of Subjects on Each Day of Chemotherapy

Groups	Weight categories and amount of drug in capsule	1st dose (1 hr before start of chemotherapy infusion)	2nd dose (3 hr after start of chemotherapy infusion)	3rd dose (8 hr after start of chemotherapy infusion)
Experimental group	20–40 kg (smaller capsules containing 167 mg)	2 capsules	2 capsules	2 capsules
	40–60 kg (bigger capsules containing 400 mg)	2 capsules	2 capsules	1 capsule
Control group	20–40 kg (smaller capsules containing 167 mg)	2 capsules	2 capsules	2 capsules
	40–60 kg (bigger capsules containing 400 mg)	2 capsules	2 capsules	1 capsule

enrolled cycles were analyzed. Patients $\geq$20 kg and $<$40 kg in weight received 6 capsules/day containing 167 mg of either ginger powder or starch powder (Total dose: 1,000 mg/day); while those $\geq$40 kg and $<$60 kg in weight received 5 capsules/day containing 400 mg of either ginger powder or starch powder (total dose: 2,000 mg) (Table I). The capsules containing both ginger powder and placebo (starch powder) were provided by Tulsi Ayurvedics & Research Pvt. Ltd (Varanasi, India).

Assessments and Interventions

The baseline assessment consisted of demographic profile and presence of nausea and vomiting. The data pertaining to nausea and vomiting were collected from each patient from days 1 to 10 of the chemotherapy cycle. In order to collect these data, patients/guardians were instructed to complete a patient diary which contained questions pertaining to grades of nausea and vomiting as measured by Edmonton's Symptom Assessment Scale (ESAS) [10–12] and National Cancer Institute (NCI) guidelines [13] respectively. In the ESAS scale, a score of zero was graded as absence of nausea, a score of 1–3 as mild, 4–7 as moderate, and 8–10 as severe nausea. Information in the diary included the number of episodes and amount of vomitus per day which was graded as per NCI guidelines. Patients were called up telephonically on the seventh and tenth day of chemotherapy so as to reinforce the recording of symptoms in the diary.

Study End Points

The study end points were the incidence and severity of acute and delayed CINV. Acute CINV was defined as nausea and vomiting occurring within 24 hr of the start of chemotherapy (days 1–4) and delayed CINV as that occurring more than 24 hr after completion of chemotherapy (days 5–10).

Statistical Analysis

Descriptive statistics were used to analyze the demographic and clinical characteristics. Severity of acute and delayed CINV among the study groups was compared by Pearson Chi-Square test. Descriptive statistics were used for comparing the incidence of CINV. All statistical analysis carried out by SPSS (version 15) and a P value of $<$0.05 was considered significant.

RESULTS

Baseline Patient Characteristics

During the study period, 61 consecutive cycles of chemotherapy in 32 patients with bone sarcoma met the inclusion criteria. Of these 60 cycles in 31 patients with bone sarcoma were randomly assigned to either oral ginger root powder capsules or placebo arm (Fig. 1). Eight patients were enrolled for 1 cycle each (8 cycles: 4 each in ginger and placebo arm), 17 patients for 2 cycles each (34 cycles: 18 cycles in 11 patients were randomized to ginger arm and 16 cycles in 11 patients to placebo arm) and 6 patients for 3 cycles each of chemotherapy (18 cycles: 8 cycles in 5 patients were randomized to ginger arm and 10 cycles in 6 patients to placebo arm). The median age of the control and experimental groups were 15.83 years (range: 9–21 years) and 15.53 years (range: 9–21 years) respectively. The baseline demographic characteristics were similar for the two treatment groups (Table II). Protocol deviation occurred in three patients in ginger arm as they could not comply with data collection procedure despite reinforcements in two patients; one patient did not comply with the intervention.

Acute CINV

Baseline observation score for nausea and vomiting was 0 for all subjects in both the groups. The incidence of acute nausea was 100% in both the groups. Acute moderate to severe nausea was observed in 28/30 (93.3%) cycles in the control group as compared to 15/27 (55.6%) cycles in the experimental group ($P = 0.003$) (Table III). There was complete absence of vomiting in 1/30 (3.3%) cycles in the control arm while no vomiting was reported in 4/27 (14.81%) cycles in the experimental arm. Moderate-severe vomiting was significantly more in the control group as compared to the experimental group [23/30 (76.7%) vs. 9/27 (33.33%) respectively ($P = 0.002$)] (Table III).

Delayed CINV

Moderate to severe delayed nausea was observed in 22/30 (73.3%) cycles in the control group as compared to 7/27 (25.9%) in the experimental group ($P < 0.001$) (Table III). In the control group, 3/30 (10%) cycles and in the experimental group 9/27 (33.3%) cycles, no delayed vomiting was reported. Moderate to severe vomiting was significantly more in the control group as compared to the experimental group [14/30 (46.7%) vs. 4/27 (14.8%) ($P = 0.022$)] (Table III).

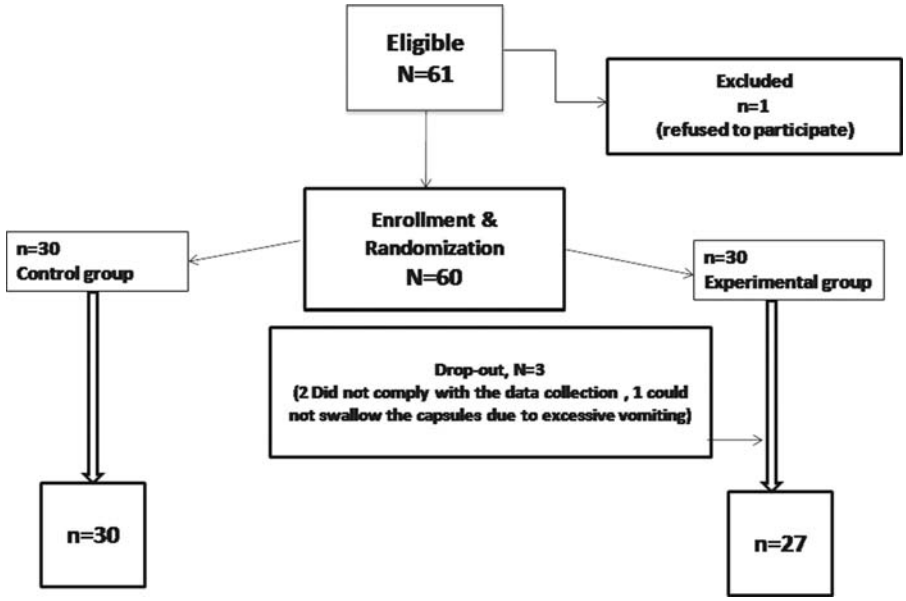

Fig. 1. Consort diagram.

TABLE II. Baseline Characteristics of Subjects in the Control (Placebo) and Experimental (Ginger) Groups (N = 60)

Variable	Study groups		*P*-Value (Pearson Chi-square test)
	Control (n = 30) (%)	Experimental (n = 30) (%)	
Age			
8–15 years	10 (33.33)	15 (50.0)	1.000
16–21 years	20 (66.67)	15 (50.0)	
Gender			
Male	16 (53.3)	24 (80.0)	0.055
Female	14 (46.7)	6 (20)	
Place of living			
Rural	11 (36.7)	11 (36.7)	1.000
Urban	19 (63.3)	19 (63.3)	
Socio-economic status			
Low	9 (30.0)	12 (40.0)	0.09
Middle	6 (20.0)	11 (36.7)	
Upper-middle	15 (50.0)	7 (23.3)	
Family type			
Nuclear	26 (86.7)	24 (80.0)	0.73
Joint	04 (13.3)	06 (20.0)	
Education			
Primary or less	13 (43.3)	17 (56.7)	0.44
Secondary	17 (56.7)	13 (43.3)	
Care giver			
Parent	29 (96.7)	28 (93.3)	1.00
Others	01 (03.3)	02 (06.7)	
Cycle of evaluation			
Cycle No. 1	7 (23.3)	8 (26.7)	0.99
Cycle No. 2	6 (20.0)	6 (20.0)	
Cycle No. 3	7 (23.3)	7 (23.3)	
≥Cycle No. 4	10 (33.4)	9 (30.0)	

TABLE III. Primary Outcome Variable

Symptom assessed	Groups (N = 57) Control (n = 30) (%)	Groups (N = 57) Experimental (n = 27) (%)	*P*-Value (Pearson Chi-square test) (comparing none-mild vs. moderate-severe)
Acute phase (days 1–4)			
CIN			
None	0 (0)	0 (0)	0.003[a]
Mild	2 (06.7)	12 (44.4)	
Moderate	6 (20)	11 (40.7)	
Severe	22 (73.3)	4 (14.8)	
CIV			
None	1 (3.3)	4 (14.8)	0.002[a]
Mild	6 (20)	14 (51.8)	
Moderate	10 (33.3)	6 (22.2)	
Severe	13 (43.3)	3 (11.1)	
Delayed phase (days 5–10)			
CIN			
None	0 (0)	6 (22.2)	<0.001[a]
Mild	8 (26.7)	14 (51.8)	
Moderate	10 (33.3)	4 (14.8)	
Severe	12 (40)	3 (11.1)	
CIV			
None	3 (10)	9 (33.3)	0.022[a]
Mild	13 (43.3)	14 (51.8)	
Moderate	8 (26.7)	3 (11.1)	
Severe	6 (20)	1 (3.7)	

[a]Signifies difference at $P < 0.05$.

Tolerability

Ginger powder and placebo capsules were convenient to administer and well-tolerated by the children and young adults. None of the subjects reported any significant adverse effects such as rash, bleeding or tachycardia with either ginger powder or placebo.

DISCUSSION

Complementary and alternative modalities in treating CINV open a new avenue in cancer treatment especially in those patients who are receiving chemotherapy with high emetogenic potential. The present study explored the effectiveness of ginger root powder as an add-on therapy over placebo along with standard treatment of CINV in patients receiving highly emetogenic chemotherapy, wherein all subjects received a uniform chemotherapy protocol, in a selected oncology outpatient unit. An accurate dose of ginger powder per kg body weight has not been established for children in previous studies; also, an empirical dosage of ginger powder was administered in adults. Likewise, we have also used an empirical dosage of 1 and 2 g/day for 3 days as an add-on therapy with chemotherapy for the subjects of the lower (20–40 kg) and higher (40–60 kg) weight categories respectively.

It was observed that ginger root powder was significantly effective in reducing the severity of both acute and delayed CINV in children and young adults [3,14]. Similar observation was found where oral encapsulated ginger and protein meals along with ginger were administered to adults receiving chemotherapy [15,16]. An animal study which studied antiemetic effect of ginger extract in cisplatin induced emesis also demonstrated that ginger is effective in reducing the severity of CINV [17]. In contrast, Zick et al. [3] had reported that ginger provides no additional benefit for reduction of the severity of acute or delayed CINV when given along with 5-HT_3 receptor antagonists and/or aprepitant in adults; however, multiple chemotherapy regimens were used in this study. In another study of cancer patients on cyclophosphamide with conventional anti-emetics, the results showed that complete control of nausea was achieved in 62% patients with ginger, 58% with metoclopramide and 86% with ondansetron when no other anti-emetics were used in any of the groups [1].

Ginger extract has been known to variably inhibit platelet aggregation [18,19]. We did not observe any rash or bleeding with ginger powder, which is less potent than the extract. However, we did not perform platelet aggregation studies to detect any subclinical toxicity related to the intervention.

Although the severity of CINV (both acute and delayed) was reduced by ginger in our study, inferential statistics could not be applied for individual categories of CINV (none, mild, moderate, and severe) and other toxicities due to the paucity of observations in each category. Therefore, the severity of nausea and vomiting were assessed cumulatively by analyzing the incidence of none and mild symptoms together in one class and moderate and severe symptoms in another. While there were more teenagers relative to younger children in the placebo arm as compared to the ginger arm, this difference did not meet statistical significance.

In conclusion, even though ginger root powder was effective in reducing the severity of acute and delayed CINV, it did not eliminate them. One of the drawbacks of our study was that the randomization was done as per cycles rather than subjects. Unlike other studies where the anti-emetic effect of ginger was assessed in patients receiving multiple regimens of chemotherapy, only those

subjects receiving a uniform regimen of chemotherapy and similar supportive treatment were enrolled in the present study. Double blind design was used as well to minimize bias in data collection. Thus, ginger root powder may be used as an add-on therapy in patients receiving chemotherapy with high emetogenic potential. There is a need to have ginger root powder available as capsules in varied dosages.

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