

## Antiemetic activity of ginger in children receiving cancer chemotherapy

Mazin M. Fawzi

Department of Pediatrics, College of Medicine, University of Mosul.

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### ABSTRACT

**Objective:** To evaluate the antiemetic effect of ginger versus metoclopramide in children receiving cancer chemotherapy.

**Methods:** A sample of 50 patients aged 6 – 14 years attending the Haematooncology unit in Ibn Al – Atheer Children's Teaching Hospital in Mosul city and receiving chemotherapy for their malignancies were included. They were randomly subdivided into 2 groups and received different types of treatment including ginger and metoclopramide.

**Results:** The study showed that cancer was more common in female than in male with male to female ratio 0.85/1. Acute lymphoblastic leukemia was the most common type of cancer and constituted 60% of the cases and it revealed that response rate was higher in those treated by ginger compared to metoclopramide (72% and 32% respectively); response was found to be higher in males than in females (86.6% and 50% respectively).

**Conclusions:** Nausea and vomiting are common problems in children receiving chemotherapy. Ginger (*Zingiber officinale*) appears to be promising in controlling these problems.

### الخلاصة

**الهدف:** تهدف الدراسة إلى البحث في التأثير المضاد للغثيان والقيء لمادة الزنجبيل مقارنة بعقار الميتوكلوبراميد عند الأطفال الذين يخضعون للعلاج الكيماوي.

**المشاركين في الدراسة:** شملت الدراسة ٥٠ طفل بعمر ٦-١٤ سنة.

**مكان الدراسة:** وحدة أمراض الدم والسرطان في مستشفى ابن الأثير التعليمي في مدينة الموصل.

**قياس المحصلة النهائية:** تم تحليل النتائج باستخدام مربع كاي ونسبة الخطورة باستخدام الحاسبة الالكترونية.

**النتائج:** أظهرت الدراسة أن نسبة الاستجابة للعلاج بمادة الزنجبيل هي أعلى مقارنة بعقار الميتوكلوبراميد (٧٢% و ٣٢%) بالتعاقب، وان هذه الاستجابة كانت أعلى عند الذكور مقارنة بالإناث (٨٦,٦% و ٥٠%) بالتعاقب، وكانت حالات السرطان أعلى نسبة لدى الإناث مقارنة بالذكور، وشكل سرطان الدم اللمفاوي الحاد أعلى نسبة بين حالات السرطان الأخرى (٦٠%).

**الاستنتاج:** في ضوء النتائج المستخلصة من الدراسة يمكن الاستنتاج بأن الغثيان والقيء يشكلان مشكلة لدى الأطفال الخاضعين للعلاج الكيماوي، ومادة الزنجبيل تبدو مشجعة في السيطرة على هذه المشاكل.

Nausea and vomiting have consistently ranked high on the list of factors most feared by patients receiving chemotherapy<sup>(1,2)</sup>, and it is an important and common problem of cancer treatment. The central nervous system

plays a critical role in the physiology of nausea and vomiting, serving as the primary site that receives and processes a variety of emetic stimuli<sup>(3)</sup>, one of them is cancer chemotherapeutic agents which act on

chemoreceptor trigger zone by dopamine or 5-hydroxy tryptamine receptor activation. Because antineoplastic agents are cell cycle dependent, their adverse effects are generally related to the proliferation kinetics of individual cell population, most susceptible are those with high rates of cell turn over<sup>(4)</sup>. Therefore chemotherapy can act peripherally causing damage in gastro intestinal mucosa and releasing serotonin from enterochromaffin cells of the small intestinal mucosa which carry sensory signals to the medulla, leading to emesis<sup>(5)</sup>. Abdominal vagal afferents appear to have the greatest relevance for chemotherapy – induced nausea and vomiting<sup>(6)</sup>. Only few studies addressing the prevention of chemotherapy induced emesis have been carried out in children. Results obtained in adults can not be applied directly to children, since metabolism and side effects of drugs may be different. When tested in children, metoclopramide, which is a valuable drug for treatment of nausea and vomiting, had only moderate efficacy and significant side effects, most notably sedation and extrapyramidal reactions<sup>(5,7)</sup>.

Over the last 2 decades, more effective and better – tolerated agents have been developed to prevent chemotherapy – induced nausea and vomiting<sup>(3)</sup>. Complementary and alternative medicine is increasing in use in the pediatric oncology population<sup>(8)</sup>. Ginger (*Zingiber officinale*) is considered a safe herbal medicine with only few and insignificant side effects<sup>(9)</sup>. The focus of this article was to compare the antiemetic effect of ginger versus metoclopramide in children receiving chemotherapy.

## Methods

In this clinical study, the sample consisted of 50 patients, 23 males and 27 females who were receiving chemotherapy, and suffering from different types of cancer (30 acute lymphoblastic leukemia, 5 acute non-lymphoblastic leukemia, 10 non-Hodgkin lymphoma, 3 neuroblastomas and 2 rhabdomyosarcomas).

They were attending pediatric hemato-oncology unit in Ibn Al – Atheer Teaching Hospital in Mosul city during the period from

may to October 2008. The selection of patients depended on the following entry criteria:

- Histologically confirmed diagnosis of cancer.
- Currently receiving chemotherapy containing any chemotherapeutic agent at any dose experiencing nausea and/or vomiting.
- Chemotherapy regimens given orally, IV, or by continuous infusion.
- Must have received at least one prior chemotherapy course containing any chemotherapy meets the following criteria.
  1. Agent is the same that is scheduled for the next round of chemotherapy.
  2. Experienced nausea and/or vomiting of any severity.
- Must be planning to receive antiemetic.
- No symptomatic brain metastases.
- No concurrent therapeutic doses of warfarin, aspirin, or heparin.
- Their age range from 6-14 years.
- No history of bleeding disorder.
- No thrombocytopenia.
- No gastric ulcer.
- Able to swallow capsule.
- No clinical evidence of current or impending bowel obstruction.

Agreements from the health authority and parents of the children were obtained.

The sample was randomly subdivided into 2 groups, each group consisted of 25 patients. Ginger and metoclopramide that were used for treatment were enclosed into empty hard gelatin capsule in order to have the same form, so that all patients received their treatment blindly. The capsules were prepared by a clinical pharmacist. The ginger was purchased from the local market (Indian ginger).

First group of patients were treated by ginger capsules orally. Dosage was calculated by adjusting the recommended adult dose to account for the child's weight. Most herbal dosages for adults are calculated on the basis of a (70 kg) adult, therefore if the child weight (20 – 25 kg), the appropriate dose of ginger for this child would be 1/3 of the adult dosage<sup>(10,11)</sup>, so each capsule was prepared to contain 500 mg of fresh ginger and to be taken

one capsule twice daily for 3 days. The second group was treated by capsules containing 10 mg of metoclopramide 3 times daily for 3 days.

Nausea was recorded by the patient and vomiting was measured by counting the number of vomiting episodes after treatment.

Studies have documented that occurrence of complete response (no nausea and vomiting episodes) is a highly accurate and reliable measure<sup>(12,13)</sup>. This outcome has also been demonstrated to correlate with the patient's perception of nausea which can be judged only by the patient and this is according to a rating scale for nausea and vomiting utilizing verbal descriptors which was used in series of assessment studies in children with cancer aged 5 – 18 years<sup>(14,15)</sup>. The improvement after treatment was signed by stopped and reduced nausea and vomiting.

Statistical analysis of data was done by using X<sup>2</sup> test to compare effects of these treatment modalities.

## Results

Fifty patients were included in this study; they were 23 males and 27 females. Their ages ranged 6-14 years. All patients received chemotherapy for treatment of cancer.

Table (1) shows the age and sex distribution of the study population; it is clear that cancer was more common in females than in males with male to female ratio of 0.85/1. Moreover the highest number of patients was in the age group 10-12 years.

Table (2) shows the distribution of cases according to the diagnosis. It is clear that ALL constituted 60% of cases of pediatric malignancies, followed by NHL: 20% of cases.

It was evident from table (3) that the response rate (stopped and reduced nausea and vomiting) was higher among the group of patients who received ginger compared to those who received metoclopramide (72% and 32% respectively), and the relative risk was 2.37 with 95% confidence interval (CI) 1.3-3.43. The differences in response between the 2 groups was statistically highly significant ( $p < 0.001$ ).

Table (4) shows the response rate to the type of medications used in the present study in male population; the table signifies a higher response rate to ginger than metoclopramide 86.6% and 40% respectively. Moreover the relative risk observed to be 3.1 with 95% confidence (CI) 1.35-7.16 and the difference between the 2 groups was statistically very highly significant ( $P < 0.001$ ). On the other hand, table (5) shows the response rate in female population. It is evident that the response rate to ginger in female population was higher than to metoclopramide (50% and 27% respectively), nevertheless this difference was statistically not significant ( $p > 0.05$ ) relative risk found to be 1.78 with 95% confidence interval (CI) 0.67-4.61.

Table (1): Distribution of patients with cancer according to age and sex.

Age groups	Male No. (%)	Female No. (%)	Total No. (%)
6 – 8 years	4 (8)	5 (10)	9 (18)
8 – 10 years	5 (10)	5 (10)	10 (20)
10 – 12 years	8 (16)	9 (18)	17 (34)
12 – 14 years	6 (12)	8 (16)	14 (28)
Total	23 (46)	27 (54)	50 (100)

Table (2): Distribution of cases of cancer according to diagnosis.

Diagnosis	Male No. (%)	Female No. (%)	Total No. (%)
ALL	16 (32)	14 (28)	30 (60)
NHL	4 (8)	6 (12)	10 (20)
AML	2 (4)	3 (6)	5 (10)
Neuroblastoma	1 (2)	2 (4)	3 (6)
Rhabdomyosarcoma	0 (0)	2 (4)	2 (4)
Total	23 (46)	27 (54)	50 (100)

ALL =acute lymphoblastic leukemia, NHL = non Hodgkin lymphoma, AML = acute myeloid leukemia.

Table (3): Distribution of cases according to mode of treatment and response rate.

Mode of treatment	Respond No %	Not respond No %	Relative risk	p. value	95% confidence interval of relative risk
Ginger	18 72	7 28	2.37	<0.001	1.3 – 3.43
metoclopramide	8 32	17 68			

Table (4): Distribution of male patients according to mode of treatment and response rate.

Mode of treatment	Respond No %	Not respond No %	Relative risk	p. value	95% confidence interval of relative risk
Ginger	13 86.6	2 13.4	3.1	<0.001	1.35 – 7.16
metoclopramide	4 40	6 60			

Table (5): Distribution of female patients according to mode of treatment and response rate.

Mode of treatment	Respond No %	Not respond No %	Relative risk	p. value	95% confidence interval of relative risk
Ginger	5 50	5 50	1.73	<0.05	0.67 – 4.61
metoclopramide	4 27	11 73			

## Discussion

A diagnosis of cancer evokes immediate fear for patients and their families, in part because cancer is a potentially fatal disease but also because cancer and its treatment are commonly associated with pain, nausea and other distressing symptoms. Pediatric oncologists have a primary role in symptoms management and should reassure patients and their families that relief of distressing symptoms is feasible in most situations <sup>(14)</sup>,

despite that nausea and vomiting continue to be significant side effect of cancer therapy <sup>(7)</sup>. Inadequately controlled emesis significantly impairs quality of life and increases the risk of patient non-compliance with therapy. Substantial progress has been made over the last decade in developing more effective and better tolerated means to prevent chemotherapy induced emesis <sup>(16)</sup>.

Acute lymphoblastic leukemia (ALL) is the most common childhood cancer<sup>(17)</sup>. The

incidence of ALL is higher among boys than girls, and this difference is greatest among pubertal children<sup>(18)</sup> and this is in agreement with the results of this study which showed that ALL constitutes 60% of cases of pediatric malignancies with higher incidence among boys (32%) than girls (28%).

Antiemetics generally are classified according to the predominant receptor on which they are proposed to act. For treatment and prevention of nausea and vomiting associated with cancer therapy, several new antiemetic agents may be combined; particularly the selective antagonists of type 3 serotonin (5-hydroxy tryptamine [5HT<sub>3</sub>]) receptor which are approved for use<sup>(19,20)</sup>.

This study describes the use of ginger which has anti nausea properties<sup>(21)</sup> for management of chemotherapy-induced emesis in children and to compare it with metoclopramide.

Ginger is one of the most commonly used herbal supplements that may be used in children over 2 years of age to treat such problem<sup>(11)</sup>, it is a member of family of plants that include cardamom and turmeric which has been used to ameliorate symptoms of nausea and vomiting. The exact mechanism of action is unclear, although it appears to inhibit serotonin (5-HT<sub>3</sub>) receptors and exert antiemetic effects at the level of CNS and GIT<sup>(21)</sup> which are the site of action of chemotherapeutic agents.

Metoclopramide is a valuable drug, useful for management of chemotherapy-induced emesis. It acts both peripherally (stimulate the release of Ach) and centrally (block D2 receptors in the chemoreceptor trigger zone). Additionally it can inhibit 5-HT<sub>3</sub> receptors.<sup>(20)</sup>

This clinical trial shows that ginger can significantly reduce nausea and vomiting induced by chemotherapy in children compared to metoclopramide, and this result was in agreement with other studies<sup>(21,23-27)</sup> which conclude that ginger can reduce nausea and vomiting of the chemotherapy and reduced use of anti emetic medications, on the other hand it is in disagreement with others<sup>(28-31)</sup>.

Another factor that is associated with increased nausea and vomiting after

chemotherapy is female gender<sup>(27,32)</sup> which was associated with more frequent nausea and vomiting and weaker response to treatment as was seen in results of this study which shows higher response rate to treatment with ginger in male than female (86.6%, 50% respectively) and this was in agreement with other studies<sup>(33-35)</sup>. Studies suggest that anticipatory nausea can occur in pediatric cancer patients and show features of a conditioned response with greater severity of anticipatory nausea for female patients than for male patients<sup>(36)</sup>. The higher responsiveness of female compared with male, both for conditioning of (anticipatory) nausea and for its latent inhibition may be explained by 2 mechanisms: a higher susceptibility to nausea and to the development of nausea and vomiting in female, and/or a higher competence of female for learning compared with male. Significant gender effects have been seen for post treatment nausea, and usually females respond more strongly with nausea. Preliminary evidence has been gathered that females are more prone to Pavlovian conditioning theory<sup>(37)</sup>.

## Conclusion

Ginger (*Zingiber officinale*) appears to be promising in controlling chemotherapy induced nausea and vomiting in children since it is less expensive and well tolerated by the patients with little side effects.

## Recommendations

- 1- Further studies are still needed to confirm the observation with a larger sample size and longer follow-up duration in children with chemotherapy-induced nausea and vomiting.
- 2- Further clinical trials are needed to evaluate the possible side effects of ginger in children.

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