Original Article

# The Effect and Safety of Olanzapine on Nausea and Vomiting in Children Receiving Moderately Emetogenic Chemotherapy

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## Abstract

**Background:** In order to improve the complete recovery of nausea and vomiting, we conducted a study with the aim of preventing acute and delayed nausea and vomiting in children undergoing moderate emetogenic chemotherapy.

**Materials and Methods:** A clinical trial study was done on 130 children received chemotherapy. Patients received olanzapine and placebo. All groups received granisetron along with dexamethasone (DEX). The severity of chemotherapy-induced nausea and vomiting (CINV) induced by chemotherapy was compared in two groups.

**Results:** The severity of nausea on the first, second, third, and fourth days was not significantly different ($P > .05$) in two groups. The number of patients without vomiting was significantly different during the first 24 hours after chemotherapy between patients in the two groups (82.3% vs 64.5%; $P = .016$).

**Conclusion:** This study showed that olanzapine, which acts as an inhibitor of neurotransmitters, had a favorable efficacy in controlling acute and delayed CINV. More studies with large sample size are needed to compare the effect of olanzapine with other agents including aprepitant and palonosetron in the prevention of CINV.

**Keywords:** Chemotherapy, nausea, olanzapine, vomiting

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## Introduction

The most common type of cancer in children under 15 years of age is leukemia, accounting for about 30–45% of childhood cancers.[1-5] The most common treatment for children with cancer is chemotherapy.[6-10] Despite its therapeutic advantages, it can adversely affect the quality of a life that can lead to refusal of the treatment by the patients.[11-15] These complications can drive the patient not to accept the treatment itself and/or to leave the treatment course uncompleted. Treatment refusal among the patients affected by chronic diseases such as cancers is common and is reported in about 50% of the cases.[16]

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The most common complication of chemotherapy is emesis which can hinder or even cut the planned treatment procedure.[17,18] The application of antinauseants is one of the widely used methods to reduce nausea and vomiting. Nowadays, effective drugs such as granisetron are in hand to control chemotherapy-induced nausea and vomiting (CINV). It is employed as the main drug in combination with steroids in most clinics. This drug, however, has several side effects including headache and reduced heart rate which can make the care of the chemotherapy patients even more difficult.[19] CINV remains a troublesome symptom in many patients.



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Olanzapine is a blocker of several neurotransmitters and is widely used to treat patients with intractable depression and schizophrenia and is widely used to treat patients with intractable depression and schizophrenia.[20,21] The efficacy of olanzapine has been shown to be a standard prophylactic regimen for controlling CINV in highly emetogenic chemotherapy (HEC)-receiving patients.[22] Recent studies have suggested the anti-nausea and anti-vomiting effects of this drug on chemotherapy adult patients.[21,23]

The control of acute CINV in children is currently possible with 5-HT-RA such as ondansetron, tropisetron, etc., in combination with or without corticosteroids.

In order to improve the complete recovery of CINV, we conducted a study with the aim of preventing acute and delayed CINV in children undergoing moderately emetogenic chemotherapy (MEC).

## Materials and Methods

We conducted a triple-blind, randomized, controlled trial. The number of samples in each group was determined to be 60 patients Figure 1. After providing fully informed consent, patients were randomly assigned, according to a centralized randomization list, to receive drugs. One investigator was appointed from the team prior to the commencement of the study to perform the randomization after recruitment. Each patient's visit sequence was entered into Excel software as an ID code. Then, using the RNAD function in the other column, a random number is automatically generated for each patient in each Excel row. Except for a trained experienced physician, blind randomization was performed for all patients, researchers, and study evaluators. Participants were outpatients. The patients with cancer received chemotherapy. The chemotherapy was MEC containing oxaliplatin, epirubicin, irinotecan, and 5-fluorouracil.[21,24-26]

### Inclusion and exclusion criteria

Inclusion criteria: (1) the patients were confirmed to have cancer by histopathological examination; (2) newly treated patients; (3) patients without a history of received chemotherapy, radiotherapy, molecular targeted therapy, or immunotherapy, etc., 6 months before the study; (4) no antipsychotic disease; and (5) ECOG performance status ≤2.

Exclusion criteria: (1) history of receiving chemotherapy and radiotherapy; (2) patients with gastrointestinal disorders, primary central nervous system disorders, hypertension, and cardiovascular disorders; (3) patients with respiratory problems, severe infection; and (4) diabetic patients.

### Antiemetic regimen

Randomization was blinded except for each site's pharmacist. All evaluations were performed by staff masked as to treatment

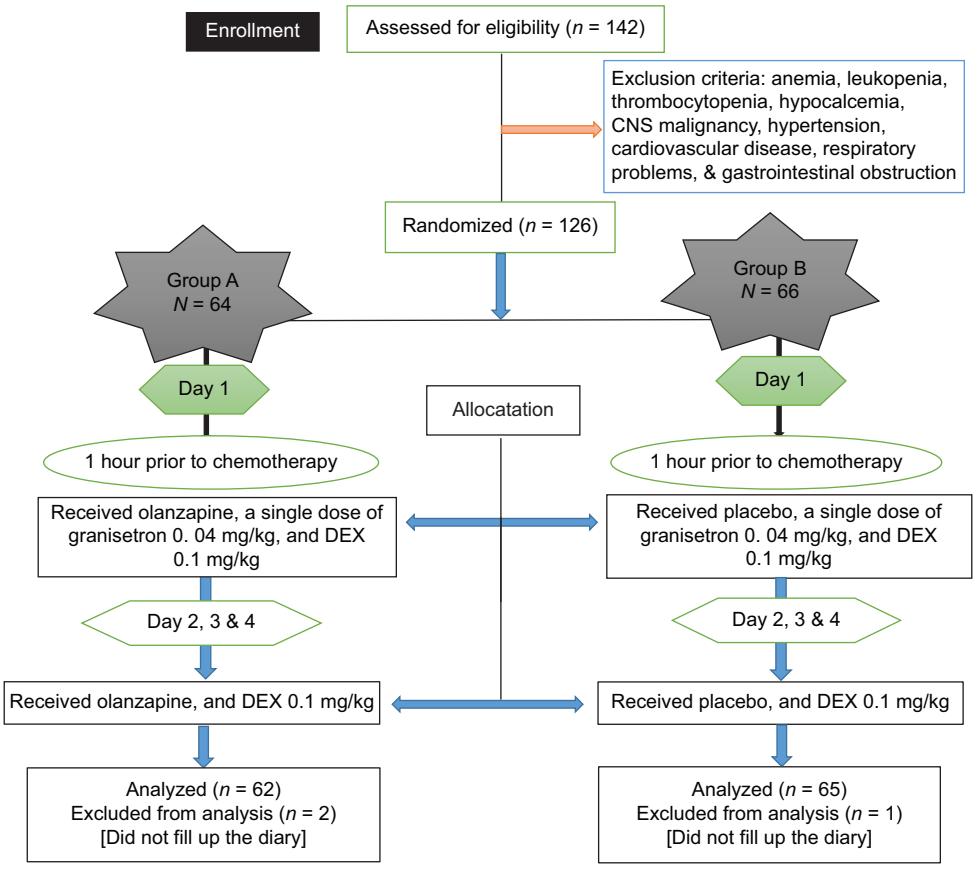


**Figure 1:** Flowchart of the study. DEX; dexamethasone

group. All patients received a single dose of granisetron 0.04 mg/kg/dose intravenously (i.v.)[27] on day 1 along with 0.15 mg/kg of DEX[28] as 15-min intravenous infusion in 100 ml normal saline 30 min on days 1–4, 1 hour before chemotherapy. In group A, 62 patients received oral olanzapine tablet at 0.14 mg/kg/dose and in group B, 64 patients received placebo capsules for four days after chemotherapy. Clinical evaluation and diagnosis of children were performed by a pediatrician.

### Efficacy parameters

The primary endpoint was complete control of nausea in the first four days after chemotherapy administration. Secondary endpoints were complete emesis control and complete control. Information on side effects after chemotherapy was recorded by telephone or in person until the end of the course.

### Statistical analysis

Statistical analyses were performed using SPSS version 18 (Inc., Chicago, IL, USA). Pearson's $\chi^2$ test and *t* test were utilized for qualitative variables and quantitative variables, respectively.

## Results

One hundred and thirty patients were included in the study. The average age at the start of the first olanzapine administration was 9.81 ± 2.78 years (range 5–15). Seventy-six patients (53.5%) were boy. Patient characteristics are presented in Table 1. Cancer types included acute lymphoid leukemia (n = 53), rhabdomyosarcoma (n = 11), Wilms tumor (n = 14), neuroblastoma (n = 12), lymphoma (n = 16), bone cancer (n = 8), acute myeloid leukemia (n = 8), and medulloblastomas (n = 4).

### Primary and secondary efficacy analysis

The complete response (CR) on the first, second, third, and fourth days was not significantly different ($P > .05$) between patients in the two groups (79.0% vs 75.0%, 72.5% vs 71.8%, 69.3% vs 73.4%, and 69.3% vs 70.3%, respectively) [Table 2]. CR was observed in group A and B patients at 72.5% and 71.8%, respectively, during the overall period ($P = 1.000$). No statistically significant difference ($P > .05$) was observed between patients in the two groups in the severity of nausea on the first, second, third, and fourth days as well as significant nausea (VAS >25 mm) and overall nausea [Table 2 and Figure 2]. A comparison of the number of patients without vomiting between patients in the two groups showed that there was a significant difference in the first 24 hours after chemotherapy (82.3% vs 64.5%, respectively; $P = .016$, Figure 3). No statistically significant difference ($P > .05$) was observed between patients in the two groups on the second, third, and fourth days as in the overall phase (87.1% vs 75.0%; $P = .084$, 90.4% vs 84.4%; $P = .447$, 92.0% vs 89.1%; $P = .583$, and 87.1% vs 79.7%; $P = .265$, respectively). Also, there was no difference in the use of antiemetic drugs in patients of the two groups ($P > .05$, Table 2, and Figure 4). No side effects were observed while taking the medication during the study [Table 3]. There was no difference in the CR of patients (79.0% vs 75.0%, 72.5% vs 71.8%, 69.3% vs 73.4%, and 69.3% vs 70.3%, respectively) on the second and third days ($P > .05$, and Figure 5).

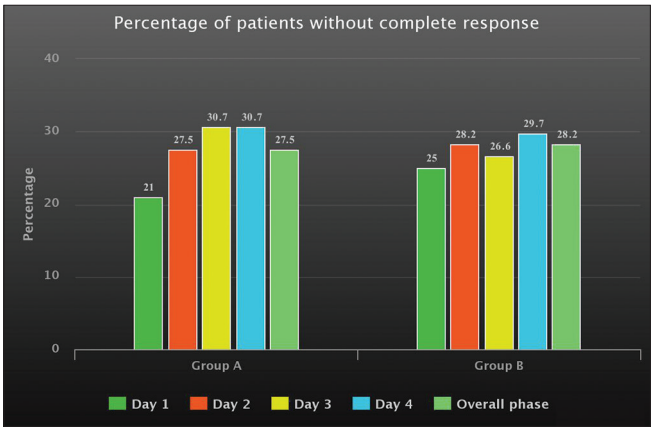


**Figure 2:** Percentage of patients without complete response

**Table 1: Clinical and demographic findings of patients**

| Characteristics | Group A (*n*=62) | Group B (*n*=64) | *P* |
|---|---|---|---|
| Gender, (%) | | | 0.189* |
| Girl | 21 (33.9) | 29 (45.3) | |
| Boy | 41 (66.1) | 35 (54.7) | |
| Age, years±SD; | 9.32±3.72 | 9.22±2.89 | 0.509† |
| Min-Max | 5-15 | 5-13 | |
| Weight, kg±SD; | 14.51±2.11 | 15.1±1.87 | 0.637† |
| Min–Max | 8.9-23.4 | 8.3-25.3 | |
| Height, cm±SD; | 93.2±1.66 | 91.1±1.15 | 0.369† |
| Min–max | 80.2-111.2 | 82.2-116.3 | |
| BMI z score | 0.46 | 0.48 | 0.958† |
| Type of cancer; (%) | | | 0.986* |
| Acute lymphoid leukemia | 27 (43.5) | 26 (40.7) | |
| Rhabdomyosarcoma | 5 (8.1) | 6 (9.3) | |
| Wilms tumor | 8 (12.9) | 6 (9.3) | |
| Neuroblastoma | 7 (11.3) | 5 (7.8) | |
| Lymphoma (Hodgkin and non-Hodgkin) | 5 (8.1) | 11 (17.2) | |
| Bone cancer | 5 (8.1) | 3 (4.7) | |
| Acute myeloid leukemia | 3 (4.8) | 5 (7.8) | |
| Medulloblastomas | 2 (3.2) | 2 (3.2) | |
| History of alcohol consumption, Yes (%) | 1 (1.6) | 2 (3.1) | 0.578* |
| Moderately emetogenic chemotherapy, (%) | | | 0.988* |
| Oxaliplatin | 20 (32.3) | 22 (34.3) | |
| Epirubicin | 16 (25.8) | 17 (26.6) | |
| Irinotecan | 15 (24.2) | 14 (21.9) | |
| 5-fluorouracil | 11 (17.7) | 11 (17.2) | |
| History of motion sickness, Yes (%) | 5 (8.0) | 3 (4.6) | 0.437* |

SD; Standard of deviation, BMI; body mass index, *n*; number. *Pearson's $\chi^2$ test was used. †Student *t* test was used

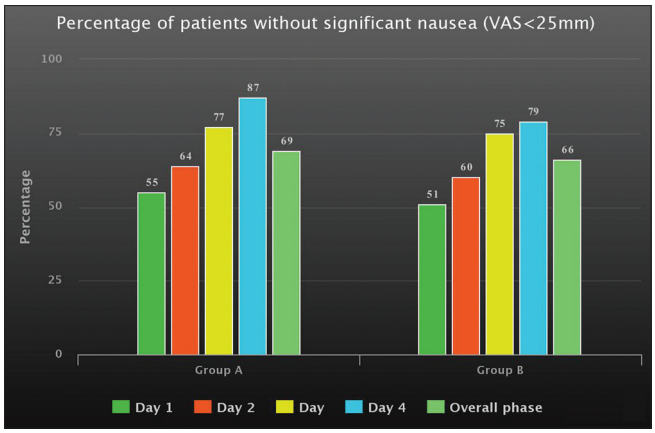


**Figure 3:** Percentage of patients without significant nausea

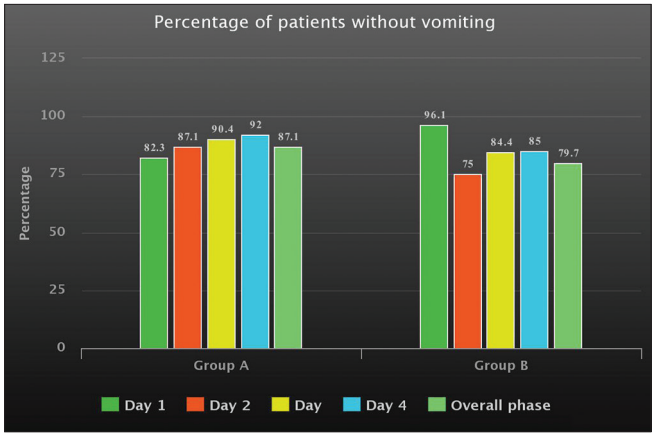


**Figure 4:** Percentage of patients without vomiting

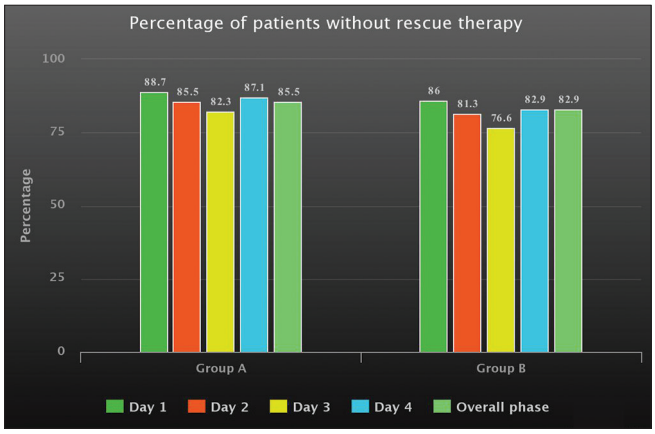


**Figure 5:** Percentage of patients without rescue therapy

## Discussion

The prevalence of vomiting and nausea was 16% in group A and 24% in group B. Olanzapine, on the other hand, can prevent against CINV in more than 84% and 76% of patients, respectively. In the valuations of CR over the period after chemotherapy, the CR rate with the addition of olanzapine to granisetron and DEX was 72.5% and 71.8% during the overall phases, which indicates a relatively favorable situation. Naik *et al*.[29] evaluated the efficacy of olanzapine in children with cancer treated with HEC. They observed a significant reduction in the number of nausea episodes among children in the olanzapine group in the acute, delayed, and overall phases. No significant difference was observed in nausea among children in group A compared with group B in the three phases: acute, delayed, and overall. In another study, Tan *et al*.[25] reported that the use of olanzapine improved the rate of CR in the prevention of CINV. Another study showed the benefit of olanzapine in adults received HEC.[30]

Navari *et al*.[31] reported that the use of the olanzapine improved the 100% CR rate. In a study about the efficacy of olanzapine

**Table 2: Status of CINV, rescue therapy, and complete response of the patients in the two groups**

| Characteristics | Group A (*n*=62) | Group B (*n*=64) | *P* |
|---|---|---|---|
| Nausea[a] (mean±SD); | | | |
| Day 1 | 43.2±17.8 | 50.1±21.6 | 0.257¶ |
| Day 2 | 37.9±19.2 | 39.9±19.7 | 0.739¶ |
| Day 3 | 22.6±11.8 | 28.0±17.8 | 0.326¶ |
| Day 4 | 15.3±12.5 | 20.3±18.8 | 0.551¶ |
| Vomiting[†] (*n*, %); | | | |
| Day 1 | 11 (17.7) | 23 (35.9) | 0.016¶ |
| Day 2 | 8 (12.9) | 16 (25.0) | 0.084¶ |
| Day 3 | 6 (9.6) | 10 (15.6) | 0.447¶ |
| Day 4 | 5 (8.0) | 7 (10.9) | 0.583¶ |
| Rescue therapy[‡] (*n*, %); | | | |
| Day 1 | 7 (11.3) | 9 (14.0) | 0.422‖ |
| Day 2 | 9 (14.5) | 12 (18.7) | 0.346‖ |
| Day 3 | 11 (17.7) | 15 (23.4) | 0.285‖ |
| Day 4 | 8 (12.9) | 11 (17.1) | 0.337‖ |
| Complete response[§] (*n*, %); | | | |
| Day 1 | 49 (79.0) | 48 (75.0) | 0.674‖ |
| Day 2 | 45 (72.5) | 46 (71.8) | 1.000‖ |
| Day 3 | 43 (69.3) | 47 (73.4) | 0.695‖ |
| Day 4 | 43 (69.3) | 45 (70.3) | 1.000‖ |

CINV; Chemotherapy-induced nausea and vomiting, VAS; Visual analog scale, *n*; number. * Severity of nausea using VAS, [†]Number patients with emesis (%), [‡]Number of patients with breakthrough medication administered, [§]Absence of vomiting and nausea, ¶Determined by using the Pearson's $\chi^2$ test (4-Day vs 1-Day), ‖Determined by using the Fisher exact test

**Table 3: Comparison of side effects between the two groups**

| Characteristics | Group A (*n*=62) | Group B (*n*=64) | Total (*n*=126) | *P* |
|---|---|---|---|---|
| Most common clinical adverse events, (%) | 7 (11.3) | 5 (7.8) | 12 (9.5) | 0.923* |
| Constipation | 6 (9.6) | 4 (6.2) | 10 (7.8) | |
| Diarrhea | 4 (6.4) | 5 (7.8) | 9 (7.1) | |
| Headache | 5 (8.1) | 4 (6.2) | 9 (7.1) | |
| Abdominal pain | 2 (3.2) | 3 (4.7) | 5 (3.4) | |
| Mucositis | 1 (1.6) | 2 (3.1) | 3 (2.4) | |
| Fatigue | | | | |

*n*; number. *Pearson's $\chi^2$ test was used

on CINV in patients received MEC and HEC, the authors found that the CR rate in the acute phase was not significantly different after MEC and HEC, but the significant level of CINV in the delayed and overall phases was significantly improved in patients received HEC or MEC.[25]

In another study, the authors reported that the combination of olanzapine with palonosetron and dexamethasone could not significantly improve the CR rate. However, they reported a clear benefit of olanzapine in the management of CINV and quality of life.[21]

In the surveys of CR over the period after HEC, Naik *et al*.[29] reported that the majority of patients received olanzapine achieved CR in the acute delayed and overall phases.

One study found that serotonin receptor antagonists, along with DEX, improved CINV in the acute phase, but that CINV remained unresolved in the delayed phase.[26,32]

This study showed that olanzapine, which acts as an inhibitor of neurotransmitters, had a favorable efficacy in controlling acute and delayed CINV.

One of the limitations of this study was the relatively small sample size, although the study was designed as a triple-blinded and placebo-controlled study. Other limitations of this study were that the effect of more than two cycles of chemotherapy was not evaluated.

## Conclusion

This study showed that olanzapine, which acts as an inhibitor of neurotransmitters, had a favorable efficacy in controlling acute and delayed CINV. More studies with large sample size are needed to compare the effect of olanzapine with other agents including aprepitant and palonosetron in the prevention of CINV.

### Ethics approval

The study has obtained approval from the Amirkabir Hospital ethical review boards (Research number 2865, May 2020) and then registered at the Iranian Registry of Clinical Trials with the ID: IRCT20150119020715N6 and ethical code: IR.ARAKMU.REC.1396.288.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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### Conflicts of interest

There are no conflicts of interest.

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